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SYMPOSIUM

The Management of Hematologic Disorders

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INTRODUCTION TO SYMPOSIUM ON THE MANAGEMENT OF HEMATOLOGIC DISORDERS

THE editors of this special number of the JOURNAL OF CHRONIC DISEASES have been fortunate in securing the generous cooperation of many of the outstanding hematologists of the country in preparing a series of up-to-date articles on the therapy of hematologic disorders. The impressive discoveries in the field of hematology which have been made in the past three or more decades have not always offered simple solutions for all the hematologic problems with which the internist and general practitioner are confronted. Thus, there is no simple cure for all anemias which can be employed indiscriminately in the treatment of anemia. There is as yet no erythropoiesis-stimulating factor which could be used to relieve anemia, no matter what the cause, nor is it likely that discoveries in this exciting field of investigation will do away with the need for good sound clinical medicine. It is still true that understanding and careful differential diagnosis are important in the management of anemias. The widely advertised claims

to the contrary notwithstanding, it is still necessary to study each patient thoroughly and to try to determine the nature of the disturbances which lie at the root of the anemia. The indiscriminate administration of vitamin B_{12}, folic acid, cobalt, and all the other vitamins and minerals which have attracted so much attention in recent years is a pernicious practice which does not relieve anemia and can even be dangerous. Anemia is a *symptom* of disease and not a disease in itself. The symptom should be recognized as a clue to the existence of disease; the latter should be uncovered and then appropriate therapy given in accordance with the cause of the anemia.

Progress in pharmacology and therapeutics in recent years has made it necessary for the physician to be more than ever on the alert for hematologic disorders which may develop in the occasional patient in association with the administration of some newly discovered and valuable therapeutic remedy. Leukopenias (agranulocytosis), thrombocytopenic purpuras, and even aplastic anemias are by no means rare consequences of drug sensitivity. Their intelligent handling and differentiation from other causes of these hematologic manifestations are essential points in their management.

In still another area, progress has been real even though cures are not available as yet. The discovery and development of chemotherapeutic agents for the leukemias have reawakened a long dormant and rather unexciting field and have stimulated investigation which should ultimately result in better forms of therapy and, one hopes, even in cure. The articles dealing with leukemia provide the reader with an up-to-date account of the therapy of leukemia and related disorders.

If a medical Rip Van Winkle were to awaken today after only a ten years' sleep, he would wish he could soon fall asleep again, for he would be most unhappy with his background in the coagulation field. Whereas he once thought he understood the process of coagulation and had learned to differentiate classical hemophilia from thrombocytopenic purpura, he is now confronted with a host of new names and new disorders as well as new tests for their differentiation. Even those who have not slept soundly for the past ten years will find the articles on the purpuras and on hemophilia and other coagulation disorders very helpful in their approach to the many intriguing hemorrhagic conditions to which man is heir.

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TREATMENT OF MEGALOBLASTIC ANEMIAS

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A SEVERE megaloblastic anemia is characterized by pronounced abnormalties of all of the formed elements of the blood. There is striking macrocytosis often associated with other aberrations of the red cells. The leukocytes are reduced in number and may display hypersegmentation of the nuclei and enlargement of the juvenile forms. In addition, the platelet count is substantially reduced. The bone marrow is hyperplastic, with red cell precursors comprising an unusually high proportion of the nucleated cells. Among these immature erythrocytes, many typical megaloblasts are seen, and there are also characteristic abnormalities of the leukocyte progenitors. This blood and marrow pattern is so unique as to be virtually pathognomonic of a deficiency of vitamin B_{12} or of folic acid. On the basis of hematologic studies, it is not possible to determine whether one or the other of these vitamins is lacking. Other clinical evidence must be employed to establish a definitive diagnosis so that appropriate therapy can be administered.

While the presence of an unequivocal megaloblastic anemia points clearly to an underlying specific vitamin deficiency, a normal blood picture by no means excludes the possibility of such a deficiency. Depletion of vitamin B_{12} may produce serious and incapacitating illness at a time when the blood and marrow appear entirely normal. Furthermore, when anemia is mild, abnormalities of the blood and marrow cells are often not pronounced. In this situation, the differentiation between megaloblastic anemia and certain other hematopoietic disorders may be difficult or impossible. Diagnostic hazards are increased by the fact that cells morphologically indistinguishable from megaloblasts are occasionally encountered in the marrow of patients with disorders unrelated to deficiencies of vitamin B_{12} or folic acid. In rare instances of leukemia, such cells have been so impressive as to lead to an erroneous diagnosis of pernicious or refractory megaloblastic anemia.[1] More often confusion has resulted from a megaloblast-like alteration in the marrow in certain instances of hemolytic anemia. Careful consideration of the clinical syndrome, use of certain laboratory investigations, and well-controlled therapeutic testing will in most instances establish the diagnosis.

Deficiency of vitamin B_{12} of a degree sufficient to produce clinical manifestations is, with rare exceptions, attributable to malabsorption of the vitamin from the gastrointestinal tract. On the other hand, folic acid deficiency may result from inadequate intake, defective absorption, increased utilization, or the action of chemical antagonists of the vitamin. The clinical disorders which result from deficiencies of these vitamins are strikingly similar, reflecting the close metabolic interrelationships of vitamin B_{12} and folic acid. Megaloblastic anemia, glossitis, and alimentary disturbances may occur as a result of a deficiency of either. The characteristic neurologic manifestations of subacute combined degeneration of the spinal cord are associated only with depletion of vitamin B_{12}. Therefore, the presence of these neurologic abnormalities is pathognomonic of vitamin B_{12} deficiency.

Laboratory procedures may provide assistance in the detection of the deficiency state and the recognition of its cause. Measurement of the concentration of vitamin B_{12} in the serum and direct measurement of its absorption employing Co^{60}-labeled vitamin B_{12} often provide a precise diagnosis.[2-4] Less specific but helpful information may be obtained by simple tests such as gastric analysis.

The demonstration of a satisfactory clinical and hematologic response to the specific agent which has been lacking provides convincing support for the diagnosis of a deficiency state. However, great caution is required in interpreting the results of such a therapeutic test. Occasional patients with the megaloblastic anemias of pregnancy or infancy, generally recognized to be due to folic acid deficiency, have been observed to respond to treatment with vitamin B_{12}.[5-8] Almost all patients with vitamin B_{12} deficiency have an initial satisfactory response to folic acid. Accordingly, the therapeutic test with vitamin B_{12} and folic acid can be relied upon to differentiate with certainty between deficiencies of these substances only if the patient fails to respond to one and then has a complete response to the other.

The important agents available for specific treatment of megaloblastic anemias are folic acid, citrovorum factor, vitamin B_{12}, and vitamin B_{12} with intrinsic factor concentrate. Folic acid may be administered orally or parenterally. The usual dose is 5 to 15 mg. per day. Orally administered folic acid appears to be effective even in those patients whose deficiency is the result of abnormal absorption. Therefore, parenteral therapy is required only when oral preparations cannot be given. Megaloblastic anemias which respond to treatment with folic acid can be as satisfactorily treated with citrovorum factor* (folinic acid) but there is no advantage in the use of the latter and its cost is much greater. The only clinical indication for use of citrovorum factor is to overcome the effects of the folic acid antagonists.[9] Citrovorum factor is much more effective than folic acid in preventing the manifestations which follow the administration of Aminopterin and related compounds. In this situation the usual dose is 3 to 6 mg.

Vitamin B_{12} (cyanocobalamin) may be administered by mouth or parenterally. Normal individuals absorb only a few micrograms even when very large

*Available as Leucovorin (Lederle).

oral doses are administered.[10] Intramuscular and intravenous injections have been administered in amounts larger than 1,000 mcg. without untoward effects. The usual parenteral dose is 15 to 50 mcg. When larger amounts are given, the excess is rapidly excreted in the urine.[11] A rare patient may display hypersensitivity reactions to the injection of concentrates of vitamin B_{12}, but crystalline vitamin B_{12} has not caused allergic manifestations. Vitamin B_{12} with intrinsic factor concentrate is administered by mouth. One U.S.P. unit is that amount which has been shown to produce adequate clinical and hematopoietic responses when given daily to patients with pernicious anemia in relapse. One U.S.P. unit contains no more than 300 mg. of intrinsic factor concentrate and no more than 15 mcg. of vitamin B_{12}. The minimum dose is one U.S.P. unit daily.

Ascorbic acid, although intimately related to folic acid metabolism, is not an important therapeutic agent in the treatment of vitamin B_{12} or folic acid deficiency states. Citrovorum factor is the physiologically active form of folic acid, and ascorbic acid is necessary for the conversion of folic acid to citrovorum factor.[12]

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PERNICIOUS ANEMIA

The most common and most important megaloblastic anemia occurring in the United States is that associated with pernicious anemia. The clinical manifestations of this disease are attributable to deficiency of vitamin B_{12} resulting from impaired absorption of the vitamin from the gastrointestinal tract.[13] The primary lesion is in the stomach, which fails to secrete "intrinsic factor," a substance required for optimal absorption of vitamin B_{12}. Since the gastric defect is permanent and not amenable to treatment, lifelong substitution therapy is required. It is necessary to distinguish between the disease *pernicious anemia* and the macrocytic anemia which is one of its manifestations. Some patients have symptoms such as glossitis, gastrointestinal disturbances, or neurologic manifestations at a time when the blood and marrow are normal. Furthermore, the disease may be entirely latent, without manifestations of any kind, for years. It is important to establish the diagnosis early in order that adequate treatment may be given to prevent involvement of the nervous system. The recognition of pernicious anemia has often been made difficult by previous administration of various therapeutic agents containing folic acid and vitamin B_{12}.[14]

Pernicious anemia, if untreated, is invariably fatal. However, there is no chronic disorder which can be more simply or more satisfactorily managed. Therapy is most reliably accomplished by parenteral injections of vitamin B_{12}. If adequate treatment is initiated before irreversible neurologic changes have occurred, complete recovery from the clinical manifestations takes place. Relapse never occurs while appropriate maintenance therapy is continued. Because of its insidious development, anemia may become profound before the patient seeks advice. Severe anemia is remarkably well tolerated by most of these individuals, but in those with underlying cardiovascular disease it may lead to angina pectoris or to heart failure.

Treatment of the Patient in Relapse.—Unless serious complicating factors such as infections or cardiac disorders are present, it is rarely necessary to transfuse patients with pernicious anemia. When the initial hematocrit value is below 15 per cent, particularly in elderly persons, a single transfusion, preferably of packed red cells, is advisable to sustain the patient until response to vitamin B_{12} can occur. The intramuscular injection of as little as 1 mcg. of vitamin B_{12} per day will produce a satisfactory clinical and hematologic response; however, this is a borderline dosage schedule which is associated with suboptimal effects in some patients.[15] In practice, much more of the vitamin is administered. When a single injection of 30 to 50 mcg. of vitamin B_{12} is given, an optimal reticulocytosis occurs with the peak almost invariably on the fifth or sixth day. Many patients will have a complete remission even though no further treatment is given. After such a large initial dose, it is not a matter of great importance which dosage schedule is followed during the early weeks of therapy, but additional injections may be given daily or several times each week to ensure that saturation of the tissues with vitamin B_{12} is accomplished. An arbitrary schedule which will certainly provide a substantial excess of the vitamin consists of the injection of 50 mcg. 3 times during the first week and once weekly thereafter until hematologic remission is complete, usually in 4 or 5 weeks. If neurologic manifestations are severe, even larger amounts may be given although there is little evidence that they have greater effect. Folic acid, iron preparations, and other antianemia agents should not be employed because they are unnecessary and because demonstration of a specific response to vitamin B_{12} constitutes additional evidence for the diagnosis. In patients with abnormal bleeding associated with severe thrombocytopenia, significant rise in the platelet count and cessation of bleeding may occur within a few days of the onset of treatment. Mental aberrations and personality disorders associated with pernicious anemia often show striking improvement within one week. On the other hand, the response of the manifestations of subacute combined degeneration is much less predictable. In some cases there is rapid symptomatic and objective neurologic recovery. Often, however, improvement occurs slowly, continuing at times for a year or more. Some patients show no change in their neurologic disorder even after prolonged and intensive therapy and others improve but have residual manifestations. Physical therapy and orthopedic procedures are often valuable adjuncts in treating severe neurologic residua.

Maintenance Treatment.—After remission has been produced, therapy with vitamin B_{12} must be continued throughout the patient's life in order to prevent recurrence. The safest and most efficient therapeutic regimen consists of the regular parenteral injection of vitamin B_{12}. The injection of 45 mcg. of vitamin B_{12} once each 6 weeks has been found to be completely effective in maintaining clinical and hematologic remission in a large group of patients with pernicious anemia,[16] some of whom have now been under observation for 8 years on this regimen. This schedule was deliberately chosen as one which probably approaches the smallest effective dose. There is no clinical evidence that larger amounts are more effective; however, the serum concentration of vitamin B_{12} may not be restored to normal unless more vitamin B_{12} is given.[2] Therefore, to provide a greater

margin of safety somewhat larger amounts may be used, for example 50 mcg. given by injection each 4 weeks. In cases in which neurologic manifestations are present it is wise to administer more frequent injections, for example, 50 mcg. each week. If it becomes clear that no further neurologic improvement is taking place, the intervals between injections may be prolonged. When patients with pernicious anemia discontinue treatment, several years may elapse before the first manifestation of recurrence can be detected.[17] Failure of relapse to occur must not be taken as evidence that continued treatment is unnecessary.

Oral Therapy.—Under appropriate circumstances sufficient vitamin B_{12} can be absorbed from the gastrointestinal tract to provide adequate therapy for patients with pernicious anemia. When large amounts of vitamin B_{12} are taken orally, the concentration gradient across the intestinal mucosa is apparently sufficiently great to cause small amounts of the vitamin to be absorbed in the absence of intrinsic factor. This absorptive mechanism is extremely inefficient, so that some patients require more than 100 times the amount of vitamin B_{12} which would be effective if given parenterally. A rather large group of patients has now been maintained in hematologic remission on a weekly oral dose (one tablet per week) of 1,000 mcg. Serum vitamin B_{12} levels in these patients tend to be lower than in a group of patients receiving 30 mcg. per month parenterally; therefore, if oral therapy with vitamin B_{12} alone is to be administered, an amount in excess of 1,000 mcg. per week should probably be used.[14]

Absorption of vitamin B_{12} from the intestine of patients with pernicious anemia is facilitated by combining small amounts of the vitamin with concentrates of intrinsic factor obtained from animal sources.[3] Such concentrates are now available in potent form and a number of acceptable preparations of vitamin B_{12} with intrinsic factor concentrate are being marketed. These products must be assayed by observing their hematopoietic effects on patients with pernicious anemia in relapse. When preparations of this type are used in the treatment of pernicious anemia, no less than 1 U.S.P. unit should be given each day. No studies have been reported in which a large group of patients with pernicious anemia has been maintained for years on a standard regimen of vitamin B_{12} with intrinsic factor concentrate. Such studies are necessary to establish that this form of therapy is satisfactory for all patients with pernicious anemia.

There are several reasons why oral therapy may be looked upon as inferior to parenteral therapy. The amount of vitamin B_{12} which can be absorbed from the intestinal tract, even by normal persons, is extremely limited. Therefore, intensive therapy by the oral route is not possible. Furthermore, the ability of patients with pernicious anemia to absorb vitamin B_{12} from the gastrointestinal tract varies considerably. This situation is in contrast to that which pertains to parenteral therapy with which there is little difference in the vitamin B_{12} requirement from patient to patient. The influence of ingested food and of other uncontrolled factors on the absorption of orally administered preparations is unknown. Oral therapy should never be used for seriously ill patients or for those with neurologic manifestations.

Other Treatment.—Liver preparations are effective in the treatment of pernicious anemia because of the vitamin B_{12} which they contain.[18] Liver extract

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is more costly than vitamin B_{12}, is less concentrated and more likely to produce pain at injection sites, and not rarely gives rise to hypersensitivity reactions. Since vitamin B_{12} is abundantly available in pure form, there appears to be no advantage in the use of crude sources. Folic acid should never be used as the primary treatment for pernicious anemia and is quite unnecessary for supplementary therapy. If folic acid is given without adequate vitamin B_{12}, hematologic remission may be accompanied by rapidly progressive neurologic disease.[19] Although achlorhydria is almost invariably present in patients with pernicious anemia, it is not the cause of the gastrointestinal symptoms which occur in this disease. There is no reason to administer hydrochloric acid as replacement therapy.

MEGALOBLASTIC ANEMIA FOLLOWING TOTAL GASTRECTOMY

Megaloblastic anemia, accompanied often by subacute combined degeneration of the spinal cord, may occur after total gastrectomy. A review of the course of 27 patients at The Johns Hopkins Hospital who had total gastrectomies performed over a 10-year period showed that all who were untreated and who survived developed anemia.[20] Macrocytosis of the red cells was noted as early as 6 months or as late as 7 years postoperatively. One or 2 years after the appearance of macrocytosis, anemia developed and was followed by megaloblastic changes in the marrow. Hematologic and clinical manifestations in these cases simulate those of pernicious anemia and respond to the administration of vitamin B_{12}. The occasional need for supplementary folic acid is probably due to the steatorrhea developing postoperatively and to the poor dietary intake of some of these patients. Iron is usually required because of the loss of blood through the gastrointestinal tract and poor absorption of iron following the gastrectomy.[20-22]

Vitamin B_{12} deficiency develops after total gastrectomy because of the resultant absence of intrinsic factor. The impaired absorption of vitamin B_{12} by these patients has been measured with methods using Co^{60}-labeled vitamin B_{12}, and can be corrected by the administration of intrinsic factor.[23] Defective vitamin B_{12} absorption and megaloblastic anemia rarely occur after subtotal gastrectomy.[24]

Treatment.—Since megaloblastic anemia seems inevitable if survival is sufficiently long, it is recommended that all patients with total gastrectomy receive parenteral vitamin B_{12} in the same dosage and frequency as in the treatment of pernicious anemia. This therapy should be initiated immediately after the surgical procedure. In addition, since almost all of these patients have intermittent blood loss from the gastrointestinal tract and impaired iron absorption, oral iron therapy should be routinely used. An occasional patient may require folic acid to maintain complete hematologic remission.

MEGALOBLASTIC ANEMIA CAUSED BY DIPHYLLOBOTHRIUM LATUM

A clinical syndrome indistinguishable from pernicious anemia occurs in a small percentage of patients infested with the fish tapeworm, *Diphyllobothrium latum*. Recent investigations indicate that the probable cause of this tapeworm anemia is the removal of dietary vitamin B_{12} by worms situated high in the

intestinal tract with resulting eventual vitamin B_{12} deficiency in the host.[25] Seen primarily in Scandinavia, human infestation by this organism occurs when inadequately salted, pickled, smoked, or raw infected fish is eaten.[26] Studies of heavily infested populations, especially in Finland, suggest that some constitutional predisposition is important in the development of the syndrome of pernicious anemia in fish tapeworm carriers.[26]

The fish tapeworm is endemic in some native strains of fish both in the United States and in Canada.[27,28] Although many cases of human infestation with this parasite have been recognized, pernicious tapeworm anemia is rarely, if ever, seen among natives of the United States. It is of interest that the majority of native cases of fish tapeworm infestation have occurred among Jewish people and it is thought that the habit of sampling gefüllte fish in preparation is an important etiologic factor in these cases.[29] Epidemiologic studies elsewhere have suggested that Jewish persons are relatively quite resistant to the development of pernicious tapeworm anemia.[26]

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Although *Diphyllobothrium latum* is the only human parasite known definitely to have an etiologic relationship to certain cases of megaloblastic anemia, a survey of reported cases of presumed pernicious anemia associated with other parasites and studies on the concentration of vitamin B_{12} within the bodies of various worms suggests that other worms, notably *Ascaris lumbricoides*, may also occasionally play a similar role.[26,30] Abnormally low vitamin B_{12} absorption has been observed in one patient who had an asymptomatic infestation with *Ascaris lumbricoides* but who showed no evidence of pernicious anemia.[4]

Treatment.—Treatment of the anemia may be undertaken equally well by the intramuscular injection of crystalline vitamin B_{12} in doses similar to those used in pernicious anemia or by ridding the patient of the worm. The latter method is effective in producing a complete hematologic remission only if the patient is receiving a diet containing adequate amounts of vitamin B_{12}.[31] It is important to make certain that the head of the worm is expelled; otherwise relapse may occur at a later date.

MEGALOBLASTIC ANEMIAS ASSOCIATED WITH DISEASES OF THE INTESTINAL TRACT

A variety of diseases involving the small intestine may lead to megaloblastic anemia in the presence or absence of free hydrochloric acid in the gastric secretions. These disorders may be loosely classified into two groups: those with anatomic abnormalities of the gastrointestinal tract leading to stagnation, and those of malabsorption.

Anatomic abnormalities of the gastrointestinal tract such as diverticula, strictures, or blind loops of the small bowel may be associated with a clinical picture indistinguishable from pernicious anemia.[32] Subacute combined degeneration is a frequent manifestation. In these patients, operative correction of the abnormality if feasible may result in hematologic and clinical improvement.[32] The administration of vitamin B_{12} is often fully effective in overcoming the manifestations of the deficiency state.[4,33] The administration of tetracycline antibiotics has also resulted in complete remissions in some cases.[34]

Studies of the absorption of radioactive vitamin B_{12} in such patients have clarified the etiology of the deficiency state. Vitamin B_{12} absorption is abnormally low and is not improved by the addition of intrinsic factor, but the administration of the tetracycline drugs may restore the absorption to normal.[33] These observations in patients and similar results obtained in experimental animals have suggested that such intestinal abnormalities cause stagnation with bacterial overgrowth. The administration of the antibiotics presumably causes destruction of intestinal organisms which previously have been depriving the host of the vitamin B_{12} normally available through the diet.[33]

Whereas the megaloblastic anemias related to structural abnormalities of the intestinal tract appear to be caused by vitamin B_{12} deficiency, those associated with the diseases of malabsorption may be attributable to deficiency of folic acid, or of both folic acid and vitamin B_{12}. The diseases comprising the sprue syndrome form a heterogeneous group all of which have in common malabsorption of many essential nutrients.[35] Regional enteritis may be associated with these same metabolic abnormalities. Megaloblastic anemia is a common accompaniment of nontropical sprue and at times is the presenting manifestation.[36] It is probable that many patients with this disease have combined deficiency of folic acid and vitamin B_{12}. Although most patients with megaloblastic anemia associated with nontropical sprue respond to folic acid or citrovorum factor alone, occasionally subacute combined degeneration develops.[35] Furthermore, studies with radioactive vitamin B_{12} have demonstrated impaired absorption in many cases of sprue.[37] Some patients with regional enteritis have likewise been noted to have impaired vitamin B_{12} absorption and may require replacement therapy with both agents.[4,38,39] In a few cases of megaloblastic anemia associated with coeliac disease the anemia responded to treatment with folic acid.[35] All of the above examples of diseases of malabsorption have one factor in common: the megaloblastic anemia and neurologic symptoms respond to appropriate treatment, but neither vitamin B_{12} nor folic acid has significant effect on the steatorrhea and other phases of malabsorption. Tropical sprue on the other hand appears to differ in that administration of either folic acid or citrovorum factor results not only in hematologic remission, but often striking and prolonged improvement of the entire disease.[35] Occasional therapeutic responses to vitamin B_{12} have been reported but are said to be much poorer and shorter-lived than those obtained with folic acid or citrovorum factor.[40]

Treatment.—

Structural abnormalities of the small intestine: Although treatment with tetracycline antibiotics may result in temporary remission, unless successful surgical correction of the basic defect is possible, it is recommended that these patients be treated throughout life with parenteral vitamin B_{12} on the same schedule as patients with pernicious anemia. Apart from the manifestations of vitamin B_{12} deficiency, the lesions are usually asymptomatic.

Nontropical sprue, coeliac disease, and regional enteritis: Maintenance therapy with parenteral vitamin B_{12} and oral folic acid is probably advisable for all such patients. Other aspects of the treatment of these diseases are beyond the scope of this report.

Tropical sprue: Adequate dietary therapy should be supplemented by treatment with folic acid at least until clinical remission is obtained.

MEGALOBLASTIC ANEMIA OF PREGNANCY AND THE PUERPERIUM

Megaloblastic anemia related to pregnancy is uncommon in the temperate zone of the United States. Reported cases have almost all occurred in the last trimester of pregnancy or in the immediate post-partum period.[7,8,41-44] The symptoms of this disorder, other than those attributed to the anemia, are quite variable.[8,41,43] Neurologic complications are rare and it is thought that patients with such symptoms have true pernicious anemia.[45] After delivery and initial therapy with folic acid, there is no tendency for the disorder to reappear unless the patient again becomes pregnant, but recurrence with subsequent pregnancies may occur.[43] The diagnosis of this anemia requires vigilance and a high index of suspicion and must rest finally upon bone marrow examination, for the peripheral blood may not show macrocytosis.[7,8,43]

The pathogenesis of the condition remains uncertain. Inadequate diet preceding and during pregnancy plays a role in some patients,[8] but reports of other patients with megaloblastic anemia of pregnancy in whom normal dietary habits were found indicate that there must be other etiologic factors.[42] Familial occurrence of the disease has been reported.[46] This disorder is clearly different from pernicious anemia. Normal results for uropepsinogen excretion, gastric mucosa biopsies, vitamin B_{12} absorption, and serum vitamin B_{12} levels have been demonstrated in a group of cases.[44] Evidence is derived, both from experimental and clinical observations with antifolic drugs, that folic acid is a necessary requirement for normal fetal growth and development.[47-49] This suggests that manifestations of folic acid deficiency in the mother may in part be due to selective concentration or utilization of available folic acid by the fetus. Some patients with megaloblastic anemia of pregnancy recover spontaneously after delivery.[41,42] The administration of vitamin B_{12} to patients with this disorder is rarely beneficial, although instances of remission following its use have been noted.[7]

Treatment.—It has been clearly established that either folic acid or citrovorum factor is an effective therapeutic agent in the treatment of megaloblastic anemia of pregnancy.[8,42-44] Although clinical response is rapid, the hematologic improvement may be much slower than that seen in pernicious anemia.[7,8] Coexisting iron deficiency may require appropriate therapy.[42]

A decrease in the incidence of this disease has been demonstrated if pregnant women are given prophylactic oral supplements of iron, folic acid, vitamin B_{12} and ascorbic acid.[8] Patients with poor dietary habits or those who previously had megaloblastic anemia of pregnancy should receive prophylactic folic acid during gestation. Further, the possible hazard of folic acid deficiency to the fetus raises the question as to whether routine prophylactic folic acid therapy during pregnancy may be justified.

MEGALOBLASTIC ANEMIA DUE TO ANTI-EPILEPTIC THERAPY

A total of 20 cases of megaloblastic anemia associated with diphenylhydantoin sodium (Dilantin) or Primidone therapy for idiopathic epilepsy have

been reported.[50-56] No specific symptoms other than those attendant upon the anemia have been described and there is no mention in the case reports of the development of subacute combined degeneration. In those patients in whom it has been studied, the serum vitamin B_{12} level, vitamin B_{12} absorption, fat absorption, and gastric mucosa biopsy have been normal. The majority of patients have had normal free hydrochloric acid in their gastric secretions. Response to folic acid indicates that the anemia is the result of folic acid deficiency. The etiology of this condition remains uncertain. It has been pointed out that there are certain structural similarities between these anti-epileptic drugs and pteroylglutamic acid, suggesting the possibility of some interference with normal folic acid metabolism.[52]

Treatment.—If the anti-epileptic drug is discontinued, only a brief period of treatment with folic acid is necessary. If, however, diphenylhydantoin or Primidone is to be continued, it is necessary to continue daily administration of folic acid to prevent subsequent hematologic relapse.

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MEGALOBLASTIC ANEMIA OF INFANCY

Megaloblastic anemia of infancy was early recognized to be distinct from pernicious anemia not only because some of the patients had normal free hydrochloric acid in the stomach but also because once a patient recovered there was no tendency for relapse to occur.[57,58] Patients who were thought to have megaloblastic anemia of infancy but who subsequently had relapses have been found to have coeliac disease, anatomic abnormalities of the small intestine, or pernicious anemia.[6,59]

Only sporadic cases of this disease were recorded until 1946, when 50 cases were described in this country and in Italy.[58,60] The sharp and substantial increase in the incidence of megaloblastic anemia of infancy during 1946 and the succeeding few years and the observations made in retrospect that this high incidence coincided with a period of time when certain proprietary artificial and vitamin C deficient diets for infants were in great vogue, led initially to the concept that dietary deficiency and, specifically, deficiency of vitamin C played an important etiologic role in this disease. Decline in incidence of this hematologic disorder in infants coinciding with the addition of vitamin C to the same proprietary feedings appeared to confirm this observation. Over the last several years many fewer but still a substantial number of cases of megaloblastic anemia have been recognized.[6]

This condition is seen chiefly in infants 8 to 14 months in age. Preceding infection, gastrointestinal symptoms, and a history of milk diet without supplementation, are common. No central nervous system manifestations have been recognized in any of the cases reported in the United States. Clinical evidences of scurvy have not been observed in this group of patients. Occasionally megaloblastic anemia of infancy has been noted in patients with kwashiorkor.[61]

Experimental work has demonstrated that a severe megaloblastic anemia can be produced in monkeys when these animals are fed diets deficient in both folic acid and ascorbic acid.[62] Major clinical differences exist, however, between this experimental megaloblastic anemia in monkeys and that spontaneously

occurring in human infants: the monkeys do not develop megaloblastic anemia until they are severely scorbutic and respond equally well to treatment with folic acid or ascorbic acid.

Treatment.—As these infants are often acutely ill at the time the clinical syndrome becomes manifest, general supportive measures, especially for complicating infections or severe diarrhea, are indicated. Furthermore, prompt treatment with folic acid as the specific hematologic agent should be initiated. In experimental studies citrovorum factor has proved equally effective,[63] but only in rare cases of this disorder will the anemia respond to vitamin B_{12}.[5,6] These patients respond poorly if at all to ascorbic acid alone, although dietary deficiencies should obviously be corrected. Once the infant has responded to the initial course of treatment with folic acid, prolonged treatment is unnecessary.

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MEGALOBLASTIC ANEMIA ASSOCIATED WITH ASCORBIC ACID DEFICIENCY IN ADULTS

Considerable debate has arisen in the past over the role of vitamin C in human hematopoiesis. The experimental production of severe human scurvy by vitamin C deficient diets has failed to produce anemia.[64] Studies of large groups of scorbutic patients have shown that anemia is not always present, and when present may be normocytic, hypochromic microcytic, or macrocytic.[65] However, in recent years a few well-documented cases of megaloblastic anemia in patients with clinical scurvy have appeared.[65,66] One of these is of particular interest in that the patient had coexistent cirrhosis of the liver.[66] The suggestion has been made that some defect in folic acid metabolism, such as might occur in liver disease, together with ascorbic acid deficiency, may be necessary to produce this disorder in man.

Treatment.—Adequate diet, with added ascorbic acid, appears to be all that is required in these patients.

NUTRITIONAL MEGALOBLASTIC ANEMIA

Individuals who subsist for long periods of time on inadequate diets may develop megaloblastic anemia as a manifestation of a deficiency state. In the United States, malnutrition of a type and degree sufficient to produce this blood disorder is not common but may be encountered particularly in chronic alcoholics and food faddists. Elderly persons who live alone and eat little but carbohydrate-containing foods may develop megaloblastic anemia. In relatively primitive or poverty-stricken societies in which pellagra and other deficiency states are common, megaloblastic anemia is not unusual. This type of anemia has been encountered in a number of patients with cirrhosis of the liver, probably because of nutritional deficiency and perhaps because of increased utilization of the vitamin.[67,68,69] In certain tropical countries malnutrition, often aggravated by infection and pregnancy, is a frequent cause of megaloblastic anemia.[54,70] In these cases the neurologic syndrome of subacute combined degeneration rarely, if ever, occurs, and it has long been known that the anemia may be refractory to treatment with refined liver extract, an excellent source of vitamin B_{12}. Most instances of nutritional megaloblastic anemia appear to be attributable

to folic acid deficiency, and satisfactory hematopoietic response to this substance is the rule.

Severe and prolonged dietary deprivation of vitamin B_{12} may be associated with manifestations of a deficiency state, but the occurrence of profound megaloblastic anemia with subacute combined degeneration solely on the basis of dietary insufficiency is rare. The best-known examples of dietary vitamin B_{12} deficiency are provided by food cultists known as Vegans who eat no foods derived from animal sources. After years of this diet, these people have been demonstrated to have low serum vitamin B_{12} concentrations. Some have developed a neurologic disorder simulating that encountered in pernicious anemia and responsive to vitamin B_{12} therapy.[50,71] It is remarkable that so few of these Vegans have been reported to develop the full-blown syndrome of pernicious anemia, suggesting that severe vitamin B_{12} deficiency is not readily produced by dietary inadequacy.

In some instances of nutritional megaloblastic anemia, low serum vitamin B_{12} levels have been observed, and response to treatment with vitamin B_{12} has been satisfactory.[72] It seems possible that in many cases of this type there is a partial deficiency of both vitamin B_{12} and of folic acid, and that treatment with either may be effective. Some patients show a slow or incomplete response to vitamin B_{12} alone, and folic acid may be required for optimal therapeutic effect.

In certain instances of megaloblastic anemia encountered in Africa, anemia has responded to treatment with orally administered penicillin.[72] In some of these cases, low serum vitamin B_{12} levels have been observed to rise after penicillin therapy. Therefore, it has been postulated that the anemia may be attributable to diets which permit intestinal growth of bacterial competitors for hematopoietic substances.

MEGALOBLASTIC ANEMIAS OF UNUSUAL ETIOLOGY

Megaloblastic Anemia Associated With Myeloid Metaplasia.—In rare instances megaloblastic anemia may be associated with myelofibrosis and myeloid metaplasia. One such case is of interest because the amount of vitamin B_{12} required to maintain remission exceeded that needed in pernicious anemia.[16] This patient, who had normal free acid in the stomach and proved myeloid metaplasia, required up to 150 mcg. of vitamin B_{12} intramuscularly weekly to control the megaloblastic anemia.

Vitamin B_{12} Binding Factor Deficiency.—A case report of a patient with long-standing macrocytic anemia but normal free acid in the gastric secretions suggests that rarely a deficiency in the vitamin B_{12} plasma binding factor may be of clinical importance.[28] This patient's anemia was refractory to treatment with vitamin B_{12} and folic acid in the usual dosage range but responded well to the administration of either 90 mcg. of vitamin B_{12} intramuscularly or to the intravenous infusion of 250 ml. of normal plasma.

SUMMARY

Megaloblastic anemia is almost always the consequence of a deficiency state. The proper management of this disorder requires the identification of

the nature of the underlying abnormality, since this dictates the choice of the specific therapeutic agent for the deficiency, the duration of treatment required, and the other therapeutic measures which may be necessary.

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TREATMENT OF IRON DEFICIENCY ANEMIA IN THE ADULT

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IRON deficiency anemia in the adult is the anemia of blood loss. This is more or less apparent depending on the intensity of bleeding. When chronic, the actual blood loss often escapes detection, and the physician makes the proper diagnosis from the demonstration of a hypochromic and microcytic anemia. With more active bleeding iron depletion may occur without morphologic changes in the erythrocytes. Thus any anemia, whether microcytic or normocytic, whether hypochromic or normochromic may be the anemia of iron deficiency, *if erythropoiesis is retarded because of inadequate available iron.* The typical morphologic changes in the red cell which are characteristic of iron deficiency anemia are found only after several months of impaired erythropoiesis due to iron lack.[1] Further, these changes, although of great value when present, are not specific and may be found in thalassemia or certain of the hemoglobinopathies. Epithelial changes of iron deficiency, i.e., spooning of the nails, cheilosis, glossitis, and esophageal webbing are rarely seen, and then only in patients with iron depletion of very long duration. Even a history of excessive menstrual bleeding or other blood loss is obtained in only about one-half of the patients with iron deficiency anemia.[2] If iron deficiency is to be recognized at its inception, there is then clearly a need for the physician to look further. For this reason certain aspects of iron metabolism in man and the pathogenesis of the depletion syndrome are summarized.

While iron excretion in man is so limited that it is unimportant (½ to 1 mg. per day), vascular damage with blood loss from the body, especially from the gastrointestinal tract, frequently results in a great loss of iron. Iron balance in the adult may then simply be stated as the balance between iron absorption and blood loss. While in the male, any blood loss is pathologic, the normal female has in menstruation a physiologic source of bleeding of considerable importance. Anemia is not necessarily the immediate result of a negative iron balance, since there are iron reserves of some 1,200 mg. which may rapidly replace red cell iron losses.[3] Whether there is significant anemia or not during the initial phase of blood loss depends on the rapidity of bleeding (Table I). As much as 500 ml. of blood loss per week may be tolerated when adequate storage iron is available to supply the activated red cell marrow.[1,4] On the other hand, once these stores of iron are exhausted, some 90 days will be required to replace by

dietary intake the iron lost from one unit of blood. These remarks serve to emphasize the *importance of iron stores in modifying the effects of blood loss.* Since there is no method of accurately measuring iron stores, the examination of the aspirated marrow for hemosiderin granules will answer the critical question of whether or not there is available iron in the body tissues.[5,6]

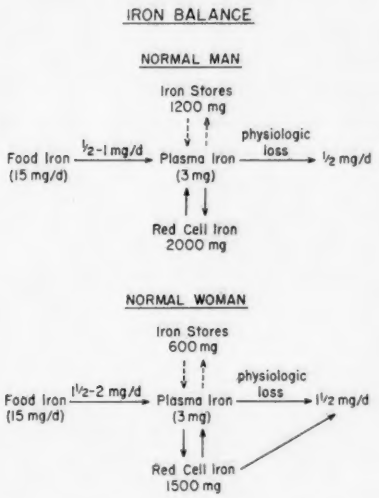

Fig. 1.—Normal iron balance in man and woman is illustrated. The exchange through absorption and physiologic loss amounts to less than 1/1,000 of the total amount daily. In the adult, blood loss is the only means of creating a significant negative balance. This may increase absorption to 3 to 4 mg. daily.

TABLE I

CONDITION	AMOUNT OF IRON (MG. PER DAY)
1. Maximal marrow requirements for erythropoiesis*	25–50
2. Mobilized from adequate stores	25–50
3. Absorbed from standard iron therapy in the iron deficient subject	25–50
4. Absorbed from standard iron therapy in normal subject	2–5
5. Absorbed from dietary iron in the iron deficient subject	3–4

* Exclusive of that turning over within the existent red cell mass.

Causes for iron deficiency in the adult other than blood loss are of secondary importance. It is true that pregnancy provides a requirement of an additional 1 mg. of iron per day as compared to the nonpregnant, menstruating female, but this is within the amount which may be absorbed from a normal diet. Likewise, absorption may be impaired in sprue, by infection, and following partial gastrectomy, but associated blood loss is generally required to produce iron deficiency anemia.

Without resorting to more detailed studies of iron metabolism, i.e., marrow and serum iron, the physician possesses the *best, single, diagnostic test in the patient's response to iron therapy.* It is indeed fortunate that there are no adjuncts required for optimal response to medicinal iron,* since this would but obscure the reason for response. A therapeutic trial with iron is not a prolonged matter. There should be an increase of more than 2 Gm. of hemoglobin per 100 ml. of blood by the end of 3 weeks.[1] The patient who does not respond to oral iron may (a) be iron deficient, but have an associated disorder blocking absorption such as sprue, or an associated disease interfering with marrow response such as infection, (b) have associated bleeding of a degree sufficient to nullify the increased blood production, or (c) have an unrelated condition simulating iron deficiency anemia such as Cooley's anemia. Response or lack of response will be similar following oral and parenteral iron in all conditions except for sprue.

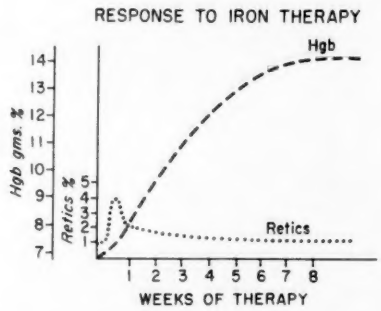

Fig. 2.—The usual response of reticulocytes and hemoglobin to treatment in the patient with iron deficiency anemia is illustrated.

There are available effective preparations of low toxicity for either oral or parenteral therapy. The ferrous salts of iron are effectively absorbed and adequately tolerated by most individuals in a dosage of 70 mg. of iron 3 times daily (0.2 Gm. exsiccated ferrous sulfate or 0.3 Gm. ferrous gluconate). Iron dextran has replaced saccharated oxide of iron as the most satisfactory parenteral iron preparation and may be given safely intramuscularly in a dosage from 100 to 500 mg. In our experience to date no serious reactions have been observed, although no parenteral therapy can be considered completely without potential hazard.

Therapy with either oral or parenteral medication should be considered in two parts: (1) *Demonstration of response.* This should be limited to the first 3 weeks of treatment either with the above daily dosage of oral iron, or a single intramuscular injection of 500 mg. of iron dextran. With either preparation the response is an increase of hemoglobin of 0.2 Gm. per day after the first 3 to 4 days (Fig. 2). Reticulocytosis is not sufficiently pronounced to be relied upon as an index of response, especially with oral iron. If a response has not occurred over 3 weeks, no further therapy is indicated. Rather, the explanation

*Adjuncts of no practical use in treatment of iron deficiency anemia include B_{12}, folic acid, copper, molybdenum, ascorbic acid, and cobalt.

for the failure should be sought. (2) *Completion of therapy.* With oral iron this is synonymous with disappearance of anemia, and therapy is generally stopped 2 to 3 weeks after the hemoglobin becomes normal, provided no further blood loss is occurring. While repletion of iron stores would seem desirable, this takes many months to accomplish by the oral route and is thus considered impractical. With parenteral iron the dose may be calculated to replenish exhausted iron stores as well.

There is an obvious difference between oral and parenteral therapy. When iron is administered by mouth, the mucosa permits absorption of an optimal amount of iron for marrow erythropoiesis but shuts off this absorption once anemia has been corrected. Thus oral iron therapy has a built-in regulator which prevents iron overload but which at the same time makes it most difficult to replenish depleted iron stores. Parenteral iron bypasses this body regulator, so that it becomes the physician's responsibility to prescribe accurately the amount needed and to avoid creating a dangerous overload. In the patient with continuous or repeated bleedings, accurate calculations of parenteral iron dosage become virtually impossible unless the patient is allowed to become periodically anemic, or unless repeated marrow examinations are performed.

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TABLE II

	THERAPY OF PREFERENCE	
	ORAL	PARENTERAL
1. Determination of Initial Response	+	+
2. General Complete Therapy		
Routine use	+	
Continuous bleeding	+	
Gastrointestinal intolerance to iron		+
Gastrointestinal disease which might be adversely affected by oral Fe		+
Need to establish iron stores		+
Malabsorption		+
Undependable patient		+

The complete treatment of the patient by these two regimens introduces further considerations. The preferred route of administration under a variety of special circumstances is indicated in Table II. Oral iron has proven an eminently satisfactory form of therapy which should be considered the method of choice in general for therapy of iron deficiency anemia. In the face of associated bleeding the dosage of 0.2 Gm. of $FeSO_4$ 3 times daily may occasionally be doubled, or tripled, with advantage.

Parenteral iron of low toxicity is too new to consider any final formulation of its role in therapy. However, on an individual patient basis, such considerations as intolerance to oral iron, noncooperation of the patient, and the possibility of impaired absorption may persuade the physician to select parenteral therapy. This is especially pertinent when time is an important factor in establishing diagnosis. Beyond this, initial treatment is largely a matter of the convenience

or preference of an injection as compared to 3 weeks' oral iron ingestion. In the patient whose source of blood loss is corrected, only one course of parenteral iron therapy will be required, and there is little need for detailed calculation of dosage. If it is the plan to create iron stores of about 1,000 mg. and to replace red cell deficit, the total dose would be somewhere between 1,500 and 4,500 mg. depending on the severity of the anemia and size of individual. In the small individual with moderate anemia a total dose of 2 Gm. is adequate; in the large individual with moderate anemia 3 Gm. may be given.

The responsibility of the physician in treatment goes beyond the management of iron deficiency. In the adult, a source of bleeding must be sought diligently, and the temporary absence of occult blood in feces should not discourage detailed roentgen study. Unsuspected peptic ulcers, diaphragmatic hernias, and neoplasms of the intestinal tract are detected as a result of this search particularly in elderly people. Occasionally, the source of gastrointestinal bleeding may be most difficult to localize. In such cases the passing of an intestinal tube with frequent aspirations to find the point of bleeding may be rewarding.

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SUMMARY

In the adult iron deficiency anemia is the result of blood loss. Its appearance may be delayed and its severity modified by the extent of storage iron and amount of iron absorbed. While a tentative diagnosis of iron deficiency may be made on various grounds, proof rests on response to a therapeutic trial of iron. Effective oral and parenteral forms of therapy are available, each with particular advantages and disadvantages. Chief among these is the advantage of mucosal regulation of iron intake when oral iron therapy is employed and the ease of creating effective iron stores when parenteral iron is used. Selection of iron therapy depends on a consideration of these various factors.

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TREATMENT OF HEMOLYTIC DISORDERS

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TREATMENT of hemolytic anemia, like that of other types of anemia should be as specific as possible. In order to direct therapy along specific lines the physician needs to make a precise diagnosis; that is, the exact type of hemolytic disorder must be determined in so far as available facilities and current knowledge will permit. First of all, however, the physician needs to recognize that anemia in a given case may be due wholly or in part to abnormally rapid destruction of red cells. A high index of suspicion will be maintained if one realizes that hemolytic disorders, in the aggregate, comprise a large group and may be encountered rather frequently at any age. Increasing frequency of diagnosis of these conditions in recent years can be attributed to the use of improved methods of detection of the specific types of hemolytic disease[1] and to demonstration of accelerated red cell destruction in a number of conditions,[2] such as cirrhosis of the liver,[3] uremia, infection, carcinomatosis, lymphoma, leukemia, and collagen disease.

Hemolytic disorders are best defined as conditions characterized by shortened life span of the red blood cells. Development of anemia, in the presence of a hemolytic state, depends upon the degree of shortening of the life span of the red cells and upon the extent of bone marrow response to demands for increased erythropoiesis. Crosby and Akeroyd[4] have estimated that red cell production can increase about seven fold, if necessary, in an adult human being. The average life span of the red cells must therefore be shortened from the normal figure of about 120 days to less than 20 days before anemia will develop, unless there is interference with the regenerative response of the marrow. Patients may unquestionably suffer from a hemolytic state without becoming anemic—a fact too little appreciated in diagnosis and treatment.

Jaundice accompanying hemolytic disorders is nearly always mild unless there are complications, as with obstruction of the common bile duct by a calculus. Since the liver has a reserve capacity for excreting bilirubin derived

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from broken-down red cells, many patients afflicted with a hemolytic disorder do not develop hyperbilirubinemia,[4] another fact too little appreciated.

The life span of red blood cells may be shortened either because of intracorpuscular abnormalities, most of which, but not all, are genetically determined, or because of the effects of extracorpuscular factors. Red cells that are "intrinsically" defective are destroyed rapidly when transfused into normal recipients while normal red cells usually, but not always, survive normally after transfusion into such patients. On the contrary, the survival of normal red cells is shortened after transfusion into patients whose own red cells are being destroyed by extracorpuscular factors or mechanisms. Transfusion experiments have done much to clarify the mechanisms of red cell destruction in the disorders under consideration.

TREATMENT OF HEMOLYTIC DISORDERS INVOLVING INTRACORPUSCULAR ABNORMALITIES

Hereditary Spherocytosis (HS) (Congenital Hemolytic Anemia).—This disorder is inherited as a mendelian dominant and is characterized by the presence in the circulating blood of spherocytes, red cells with abnormally high thickness: diameter ratio. These spherocytes are indistinguishable morphologically from those encountered in certain of the acquired hemolytic states. However, HS red cells can be differentiated from other types of spherocytes by measuring the rate of spontaneous autohemolysis during incubation of sterile defibrinated blood at 37° C. in the presence of certain additives, especially glucose, lactic acid, adenosine, and inosine.[5,6] HS cells tend to become trapped in the splenic pulp,[7,8] possibly because of their abnormal thickness, and are thus removed from active circulation. Within the spleen they undergo lysis, quite likely by processes similar to those observed during incubation in vitro. Prankerd, Altman, and Tabechian[9,10] and Motulsky and associates[11] have demonstrated abnormalities of intermediary metabolism of carbohydrate in HS cells, resulting in slow regeneration of high-energy phosphate bonds. It remains to be determined whether the genetically determined abnormality in these cells is one of structure, with secondary abnormalities in metabolism, or one of metabolism (possibly an enzyme deficiency) which might in turn be responsible for changes in shape.

In any event, it seems reasonable to postulate that HS red cells may have a "metabolic handicap" which becomes manifest when they are trapped in the spleen. Once the spleen is removed, the life span of these cells is normal or only moderately shortened despite persistence of the structural and metabolic abnormalities. Perhaps this is due to the fact that after splenectomy the red cells have continuous access to substrate for glycolysis, so that the metabolic handicap is no longer of consequence. There is nearly always prompt, complete, and permanent abatement of anemia and jaundice after splenectomy (Fig. 1). In few other chronic hematologic disorders can the surgeon promise the patient so much! Splenectomy should therefore be performed in all but the mildest cases unless there are complications, such as senility, heart disease, or malignancy, which would increase the surgical risk or shorten life expectancy.

Splenectomy may be justified even in patients having neither anemia nor jaundice, because most mildly affected HS patients feel distinctly better after

splenectomy and because they are spared the threats of crises and of the development of gallstones. It is our practice to recommend operation in nearly all cases once the diagnosis has been firmly established, but we do not press the issue if the patient claims to be asymptomatic. Whenever a new case is found, all available relatives are examined so that other afflicted members of the family can be offered the benefits of surgery. Because of the favorable prognosis in this disease, we do not advise restricted procreation, but we recommend that each child of an affected parent be examined within a few months after birth. If the infant's blood is normal, the parents can be reassured. If spherocytosis is found, splenectomy should be contemplated and performed at the age of 4 or 5 years, or earlier if crisis occurs or if growth and development are not normal. The experience of Smith and associates[12,13] suggests that splenectomy in early childhood may cause increased susceptibility to infection. On the other hand, if splenectomy is delayed beyond the age of 5 years, gallstones may form,[14] crises may occur, growth and development may be impaired, and absenteeism from school may become a problem (Fig. 1).

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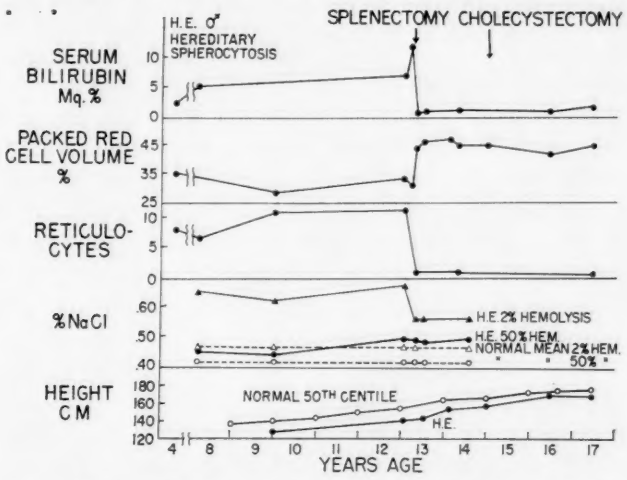

Fig. 1—Representative case of hereditary spherocytosis in which splenectomy was not permitted by parents until patient was 13 years old. By that time gallstones had formed, the boy tired easily, was frequently absent from school, and his height was considerably below the 50-centile for his age. Response to splenectomy was prompt and sustained, despite the usual persistence of spherocytosis as reflected in osmotic fragility of the red cells. The lateral plots of osmotic fragility show the concentrations of NaCl in which 2 per cent and 50 per cent hemolysis of red cells occurred.

During the past 10 years we have studied 65 cases of hereditary spherocytosis drawn from an area with a population of about one million persons. The hemoglobin and packed red cell volume were within normal limits in 6 of these cases and the serum bilirubin concentration was below 1.0 mg. per 100 ml. in 7. Forty-two of the patients investigated in our laboratory have been splenectomized in hospitals in the Rochester area, with one fatality, and with gratifying results in each of the other 41 cases. In no case has there been persistence or recurrence of anemia after splenectomy; slight hyperbilirubinemia persisted in one patient and recurred in one (Fig. 1).

The practice of squeezing the spleen at operation to force red cells from the pulp and sinusoids into the splenic vein (autotransfusion) should be abandoned. Red cells trapped in the spleen have much greater osmotic fragility than those in the peripheral circulation.[7,8] They should therefore be removed with the spleen and not forced into the circulation where they will probably remain viable for a relatively short time. If gallstones are present at the time of splenectomy, cholecystectomy may be performed during the same operation. In most cases, however, it seems better judgment to remove the gall bladder at a later date after the patient has recovered from the splenectomy.

Transfusion is unnecessary except during crises or in preparing the more severely anemic patients for splenectomy. Splenectomy can usually be performed without transfusion because anemia is seldom severe and the patients are usually well adjusted to the anemia. The hemoglobin and packed red cell volume rise rapidly after operation because the bone marrow is hyperplastic. Crises, or sudden increase in severity of anemia, may be due to failure of erythropoiesis or to acceleration of hemolysis, quite likely caused by extracorpuscular factors in some cases.[15] Transfusions may be lifesaving under these circumstances. Splenectomy should be performed as soon as the patient in crisis can be suitably prepared for surgery. Since crises may be associated with infection, antibacterial therapy may be indicated.

Chronic Nonhereditary Spherocytosis.—Chronic spherocytosis, in the absence of demonstrable autoantibodies, is by no means always hereditary. Gene penetrance or expression for hereditary spherocytosis is variable and sometimes is so feeble as to be undetectable by methods currently available. We may thus explain normal hematologic findings in both parents and other available relatives of some patients who nevertheless have the hereditary disorder. In addition, however, we have encountered at least 2 other types of chronic spherocytosis, both nonhereditary as far as we can determine. In one type, of which we have observed 3 examples, the hematologic findings prior to splenectomy were like those of HS, but within a few months after splenectomy abnormalities of the red cells could no longer be detected.[16] In the other type, of which we have also encountered 3 cases, the hematologic findings prior to splenectomy were like those of HS, except that the results of studies on autohemolysis were quite different from those of the hereditary disorder. After splenectomy, the effects of various additives on autohemolysis were the same as in HS.[5,6]

All 6 of these patients appeared to be benefited by splenectomy to the same extent as HS patients, yet the more detailed laboratory studies indicate that they were suffering from spherocytosis of different types, apparently nonhereditary. We conclude that splenectomy is indicated in most cases of chronic spherocytosis, unless associated with autoantibodies or with an underlying disease such as leukemia or myeloid metaplasia; even in these instances splenectomy may at times be justified. If affected relatives cannot be found or if tests show that the spherocytosis is atypical, benefit from splenectomy cannot be guaranteed, as it can in HS. Nevertheless, splenectomy seems justified in most of these cases.

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We have been impressed with the degree and persistence of spherocytosis in certain of the myeloproliferative disorders, especially myeloid metaplasia (in the absence of demonstrable autoantibodies). The effect of glucose and changes in pH on the rate of in vitro autohemolysis of red cells in these cases is quite different from that of HS cells.[5,6] These and other studies to be reported point to striking biochemical differences between the spherocytes of myeloid metaplasia and the hereditary spherocytes. Our experience, and that reported from other clinics, with splenectomy in spherocytic anemia accompanying myeloid metaplasia is too meager to serve as a basis for assessing the value of the operation.

Hereditary Elliptocytosis.—Elliptocytosis is inherited as a mendelian dominant and is usually a harmless condition. In some cases, however, the life span of the red cells is shortened and anemia may develop if the bone marrow does not adequately compensate. In such cases the hemolytic anemia can only rarely be attributed to homozygosity. Motulsky and associates[17] have suggested that hemolysis may be determined by a combination of the elliptocytic trait with another gene that cannot be detected by available methods. The hemolytic anemia is largely corrected by splenectomy in some cases but indications for splenectomy are not yet well established. We would recommend splenectomy if the patient with elliptocytosis developed hemolytic anemia, particularly if fragmentation spherocytes were found together with elliptocytes in the blood smears, or if the spleen were enlarged.

"Symptomatic ovalocytosis," which is found in a number of different types of anemia, both macrocytic and microcytic, should not be confused with hereditary elliptocytosis.[18]

Thalassemia (Mediterranean Anemia, Cooley's Anemia).—In thalassemia major, the homozygous state,[18] anemia is probably due chiefly to defective hemoglobin formation, but since the life span of the most defective of the red cells is substantially reduced, this disease can properly be listed among hemolytic disorders. Kaplan and Zuelzer,[19] Hamilton, Sheets, and DeGowin,[20] and others have shown that red cells from such patients have shortened survival when transfused into normal recipients. It is of interest, however, that only a portion (25 to 50 per cent) of the red cell population disappeared rapidly after such transfusions. Transfusion of normal, sedimented red cells (unwashed) to patients with thalassemia major is indicated when the chronic state is complicated by infection, major surgical procedures or trauma. Transfusion of normal red cells at regular intervals in an effort to maintain the hemoglobin concentration at 8 to 9 Gm. per 100 ml. instead of 5 to 6 Gm. may be justified in selected cases to promote growth and development, to relieve symptoms of severe anemia, and to permit a wider range of physical activity. The long-range benefits of such therapy have not yet been adequately evaluated.[21] Repeated transfusions over a period of years can be expected to cause extensive hemosiderosis and may result in the development of isoantibodies.

Normal transfused red cells may disappear rapidly from the circulation of these patients, even in the absence of demonstrable isoantibodies (or autoantibodies). In such cases hypersplenism may be responsible for destruction of

donated red cells and may accelerate the destruction of the patient's inherently defective, autogenous red cells. Under these circumstances, survival of donated cells, and probably autogenous red cells, may be substantially increased after splenectomy.[12,22] Splenectomy may also be justified if the greatly enlarged spleen encroaches seriously upon organs in the abdomen or pelvis.

Hemoglobinopathies.—In sickle cell disease (homozygous state) the life span of the red cells containing abnormal (S) hemoglobin is short, while normal transfused red cells usually survive normally. As in thalassemia major, transfusions may be needed to sustain life during periods of severe anemia or stress.[23] Chernoff, Shapleigh, and Moore[24] reported that 6 sicklemic patients with typical ulcers of the leg responded with rapid healing of the lesions when treated with bed rest, local applications, and blood transfusions sufficient to maintain the hemoglobin at nearly normal concentration. Aplastic crises,[25,26] which are usually precipitated by infection, are best treated by use of appropriate antibacterial agents and by transfusion. Periodic transfusions in the absence of severe anemia or complications are probably not justified. Anemia may become less severe after splenectomy, especially when an enlarged spleen is removed during the early years of life. The spleen tends to become smaller with age, probably due to repeated infarction. Splenectomy appears to be less frequently indicated in sickle cell disease than in thalassemia major, but further experience may lead to different conclusions. Reinhard, Moore, Dubach, and Wade[27] showed that prolonged breathing of 80 to 100 per cent oxygen failed to inhibit hemolysis or to relieve pain; their patients with sickle cell disease actually became more anemic because of inhibited erythropoiesis. Smith, Rosenblatt, and Bedo[28] reported that abdominal pain was relieved in 7 children after administration of the vasodilator, Priscoline, which was given on the assumption that pain was due to vascular spasm.

Patients with sickle cell trait (heterozygous state) do not suffer from hemolytic anemia but may develop vascular occlusions causing splenic and renal infarction, due to sickling of their red cells at high altitudes.[29] Ascent should not be undertaken without precaution to prevent hypoxia. The same advice should be given to persons having the sickling trait in combination with thalassemia or with other hemoglobinopathies (i.e., hemoglobin C, D, etc.).

Sickle cell thalassemia disease, or microdrepanocytic anemia, is usually less severe than sickle cell disease but is nevertheless a serious disorder. Management is about the same as in sickle cell disease. Sickle cell hemoglobin-hemoglobin-C disease and sickle cell hemoglobin-hemoglobin-D disease and hemoglobin-C disease (homozygous state) are still less severe; transfusion may be indicated during critical periods. The other known hemoglobinopathies seldom require treatment.

Congenital Nonspherocytic Hemolytic Anemias.—The pertinent facts regarding this heterogeneous group of anemias are well summarized by Dacie.[1] Clinical and hematologic findings in afflicted families have been described by a number of investigators. Other observers have encountered individual cases in which the hemolytic disorder was apparently congenital, but all relatives examined were hematologically normal. Varying degrees of macrocytosis,

ovalocytosis, and punctate basophilia are described; osmotic fragility is normal. Selwyn and Dacie[30] have defined 2 distinct types on the basis of in vitro autohemolysis, rate of glucose utilization, and effect of glucose on rate of autohemolysis. It seems likely that further studies will help to define still other types of congenital nonspherocytic hemolytic anemias and to explain the hemolytic mechanisms involved. It is already clear that splenectomy is of little or no benefit to these patients. Therapy is at present limited to transfusion of normal red cells during periods of severe anemia or stress.

Nonspherocytic hemolytic anemia may be demonstrable in association with congenital porphyria (porphyria erythropoietica). In such cases splenectomy may be followed by amelioration of both anemia and photosensitivity,[31,32] but lack of benefit from splenectomy has been reported in one case.[33]

Paroxysmal Nocturnal Hemoglobinuria (PNH).—The nature and etiology of the abnormality of the red cells in this rare and fascinating disease are unknown. The plasma components necessary for either in vivo or in vitro hemolysis of PNH cells are present in normal plasma as well as in PNH plasma. Observations recently summarized by Crosby[34] suggest that the delicate balance of hemolytic factors and inhibitors in the plasma is upset during sleep with the result that hemolysis is accelerated. Hemolysis may also be markedly accelerated by operations, febrile illness, or by transfusion of whole blood. Many patients with PNH have been splenectomized but rarely with benefit; the operative mortality is high because hemolysis may be accelerated in the early postoperative period.

Ham[35] produced temporary decrease in hemoglobinemia by administration of sodium bicarbonate to 2 patients, but rapid hemolysis occurred when therapy was discontinued. Crosby and Dameshek[36] had similar experience with Dicumarol and reported that heparin, given with a blood transfusion, appeared to cause a severe hemolytic reaction. ACTH, cortisone, and epinephrine have been used without significant benefit. Cervoni[37] has recently observed deceleration of hemolysis after administration of dextran; this form of therapy deserves further investigation.

Transfusion of washed normal red cells is indicated during periods of severe anemia or stress. If significant quantities of normal red cells are transfused, cessation of hemoglobinuria usually follows because erythropoiesis is suppressed and the proportion of readily hemolyzable cells in the circulation becomes relatively small. Some PNH patients tolerate whole blood but others experience hemolytic reactions, apparently due to constituents of normal plasma.[1] Group O whole blood or plasma (from "universal" donors) should never be given to PNH patients of blood groups A, B, or AB because of the anti-A and anti-B isoantibodies in normal group O plasma will readily hemolyze such PNH red cells.[1] Fortunately, some PNH patients have only moderate anemia and seldom require transfusion.

These patients may lose considerable quantities of iron in the urine (3 to 16 mg. per day[1]) and may thus become iron deficient. This is about the only hemolytic disorder in which iron therapy is sometimes indicated, even when there is no blood loss.

TREATMENT OF HEMOLYTIC DISORDERS INVOLVING EXTRACORPUSCULAR ABNORMALITIES

Autoimmune Hemolytic Disease (Acquired Hemolytic Anemia).—This is a heterogeneous group of disorders which is difficult to define but can best be discussed as a group from the standpoint of therapy. In our experience and that of others,[38,39] about 50 to 60 per cent of the cases included in this category are apparently idiopathic and the remainder are associated with an underlying disease such as lymphocytic leukemia, lymphoma, or collagen disease. There is still disagreement as to the nature of the so-called "autoantibodies" and of the antigenic stimulus for their production.[1] With due respect for the present state of ignorance, it seems reasonable to use the terms "autoantibodies" and "autoimmunization," at least as a matter of convenience. Methods currently used for detection and quantitation of autoantibodies attached to red cells and in the blood serum are well summarized by Dacie.[1] In both idiopathic and symptomatic cases there is wide variation in serologic behavior of the antibodies, especially with regard to thermal amplitude, specificity, capacity to render normal red cells agglutinable by antiglobulin serum and to hemolyze normal or PNH red cells treated with enzymes, such as trypsin.

In this group of hemolytic disorders, as in most of those previously discussed in this paper, therapy has in the past been limited chiefly to judicious blood transfusion and to splenectomy in certain refractory cases. Since 1950, however, the use of adrenocorticotropic hormone (ACTH) and cortisone (or related steroids) has proved highly effective and is now considered worthy of trial in nearly all cases once the diagnosis is established, in so far as it can be established within this heterogeneous group. The mechanism of action of ACTH and cortisone is not yet clear. The titer of circulating autoantibody usually decreases after prolonged administration of hormone, but remission may occur before such decrease can be detected. It seems possible that cortisone and related steroids may also interfere with the hemolytic effect of the antibodies on the red cells.

Response to administration of ACTH or cortisone is somewhat more satisfactory in idiopathic than in symptomatic cases but dramatically beneficial results are seen in both groups. ACTH and cortisone seem to be equally effective in most cases, but there may be exceptions.[1] One of our patients responded well to the use of ACTH, but failed to respond to oral administration of cortisone when hemolytic anemia recurred after 3 months of apparent remission. Prednisone (Meticorten) is probably as effective as cortisone and its exhibition causes less retention of sodium and water.

The largest reported experience with treatment of autoimmune hemolytic anemia is that of Dameshek and Komninos[38] who recently described their observations on 43 consecutive cases treated with ACTH or steroid hormone. Our own experience (to be reported separately in detail) has been quite similar, except that we have used, or found it necessary to use, maintenance therapy for shorter periods of time than did these authors and we have been less hesitant to recommend splenectomy in refractory cases. During the period 1946 to 1956 we have studied 44 patients, 35 of whom have received hormone therapy since

our first patient was treated with ACTH in February, 1950.[40] The 9 most recently observed patients have been treated with prednisone. Eighteen of our patients have been splenectomized, 9 prior to February, 1950, and only 9 since that date.

On the basis of the results of Dameshek and Komninos, those of Sacks, Workman, and Jahn[39] and the results in our clinic, one may conclude that about two-thirds of patients treated intensively with ACTH or steroids experience complete relief from anemia; about one-fourth of the patients enjoy partial remission, and about 5 to 10 per cent are relatively refractory. Varying degrees of relapse occur in about one-half to two-thirds of nonsplenectomized cases, and in about one-third of splenectomized cases. Evaluation of treatment is difficult because of naturally occurring fluctuations in hemolytic activity, as illustrated in Fig. 2, and because many of the patients ultimately succumb to the disease with which the hemolytic disorder is associated.

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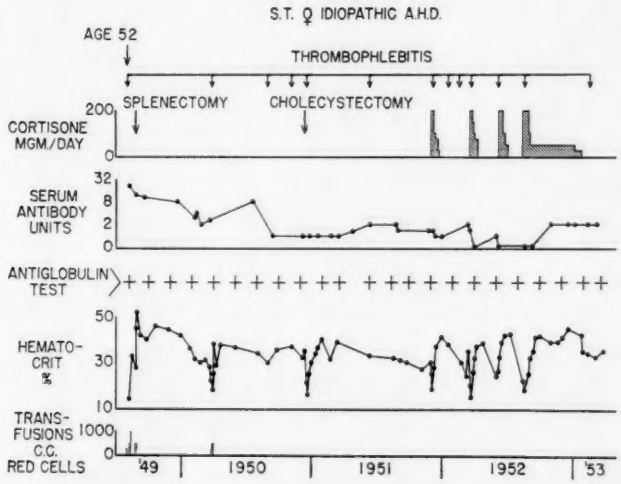

Fig. 2—Principal findings in an illustrative case of idiopathic autoimmune hemolytic disease. Serum antibody units recorded here and in Fig. 3 are reciprocals of the dilution of the patient's serum causing "50 per cent agglutination" of trypsin-treated normal red cells. The 50 per cent end points were computed by the method of Heden.[41] The patient's red cells remained directly agglutinable by antiglobulin serum throughout the period of observation (results expressed qualitatively by + signs). Note that substantial remission occurred without administration of cortisone after each of the 2 relapses in 1950. From 1954 to 1957 this patient was examined infrequently but was apparently in a state of remission from hemolysis despite lack of therapy.

Presence of an underlying disease should be suspected whenever autoimmune hemolytic anemia is encountered, and suspicion should be maintained for long periods even when there is no apparent hemolysis. Fig. 3 shows the principal findings in one of our patients in whom reticulum cell sarcoma first became evident 7 years after splenectomy had been performed for hemolytic anemia. Re-examination of the sections of spleen revealed abnormal lymphoid hyperplasia, thus indicating that lymphoma was probably present at the time of operation, even though the findings were not sufficient to support a diagnosis at

that time. Additional information concerning this patient and other chronic cases of autoimmune hemolytic disease studied in our clinic has been published separately.[42]

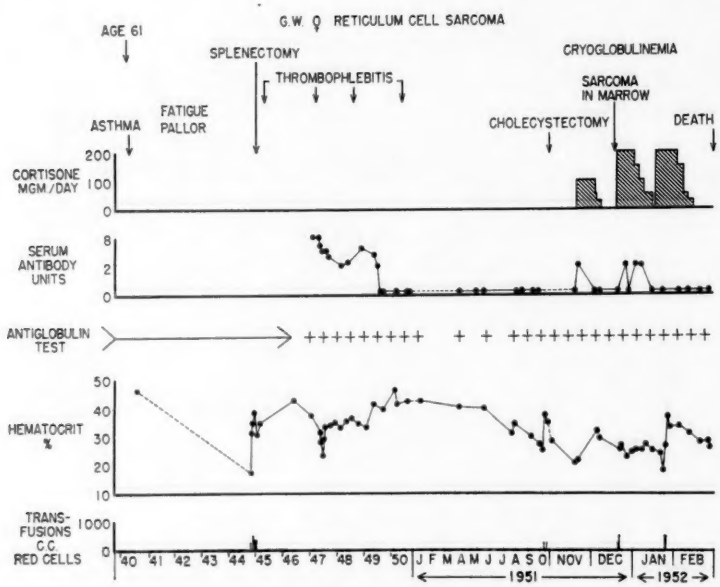

Fig. 3—Principal findings in case of autoimmune hemolytic anemia in which presence of reticulum cell sarcoma ultimately became evident. Note that remission occurred without therapy following relapse in 1947.

Our current program of therapy is as follows. Prednisone is given by mouth every 6 to 8 hours in doses of 30 to 40 mg. per day or cortisone in doses of 150 to 200 mg. per day. The dose is varied in accordance with estimated severity of the hemolytic process, body weight, and presence of complications such as heart failure or diabetes. Children are usually given larger doses per Kg. of body weight. Critically ill patients are treated initially by administration of 40 U.S.P. units of ACTH intravenously by drip over a period of 8 to 12 hours each day; hydrocortisone in doses of 200 to 300 mg. is also given intravenously on the first day, after which prednisone or cortisone is given by mouth if possible. Use of ACTH is usually discontinued after the second or third day unless the patient fails to respond to prednisone or cortisone. Eighty milligrams of prednisone or 400 mg. of cortisone may be given each day if necessary to produce remission in refractory cases. The dose of steroid is reduced gradually when the volume of packed red cells rises above 30 per cent, and the lowest possible maintenance dose is determined. Use of steroid has ultimately been discontinued in all but one of our patients, usually after 1 to 6 months of therapy.

Although splenectomy is less frequently necessary now than prior to the advent of ACTH and cortisone therapy, it is probably still justified if hemolysis persists or recurs to a serious extent despite administration of ACTH or steroid.

Data are lacking on apparent benefit from splenectomy in relation to weight of the spleen. We would nevertheless be reluctant to urge splenectomy if the spleen could not be palpated readily. Deceleration of hemolysis after splenectomy has been attributed to removal of a site of antibody production and/or to loss of an organ in which red cells may be destroyed by phagocytosis or as a consequence of stagnation and hemagglutination.[1] Failure of splenectomy has been attributed to persistence in the circulation of relatively large amounts of autoantibody capable of destroying red cells in the absence of the spleen. Despite much study, the role of the spleen in the various forms of autoimmune hemolytic disease is by no means clear.

Dameshek and Reeves[43] have reported 2 cases of occult lupus erythematosus, one presenting an autoimmune hemolytic anemia and the other as idiopathic thrombocytopenic purpura, in which clinically evident lupus developed after splenectomy. L. E. tests had been negative prior to operation but became positive afterward. These authors suggest that the spleen may inhibit progress of the disease. Further observations of this sort will be awaited with interest.

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Transfusion of sedimented (usually unwashed) normal red cells is necessary if the volume of packed red cells falls below 15 to 20 per cent (hemoglobin 5 to 7 Gm. per cent) or if the patient is being prepared for splenectomy or other major operation. Decision about transfusion is influenced by the extent to which the patient adjusts to anemia, but in any case the hemoglobin and/or volume of packed red cells should be determined frequently since anemia may become rapidly more severe during hemolytic crises. Our experience, and that of other observers, reveals that during periods of active hemolysis the patient's autogenous red cells, which are relatively young (late normoblasts, reticulocytes, and mature red cells only a few days old), are more resistant to destruction than are the older red cells transfused from normal donors. Transfusion tends to suppress erythropoiesis and also introduces an older and more readily hemolyzed population of red cells into the patient's circulation. Hemolysis may thus be accelerated after transfusion and may at times cause a substantial increase in the concentration of hemoglobin in the patient's plasma. This consequence, as well as the inevitable hazards of isoimmunization, should be taken into account whenever transfusion of such patients is contemplated. The hazards of isoimmunization are relatively great in patients with autoimmune hemolytic disease because isoantibodies develop readily after transfusion and their detection may be complicated by the presence of autoantibodies. The patient's red cells should be typed as completely as possible prior to the first transfusion.

If hemolysis is due to cold agglutinins or hemolysins, the patient should be advised to avoid chilling, or even exposure of the extremities, in so far as possible. Cold hemolysins of the Donath-Landsteiner type are frequently, but not always, associated with syphilis, which deserves separate treatment.

Hemolytic Anemia Associated With Leukemia, Lymphoma, Myeloma, Carcinomatosis.—Shortened life span of the patient's red cells as well as of transfused normal red cells has been demonstrated in patients with various types of malignant disease, even in the absence of detectable autoantibodies. Extracorpuscular factors are probably responsible for red cell destruction in a large share

TABLE I. CURRENTLY RECOMMENDED THERAPY OF CHRONIC HEMOLYTIC DISORDERS

	TRANSFUSION OF SEDIMENTED RED CELLS	SPLENECTOMY	ACTH CORTISONE HYDROCORTISONE OR PREDNISONE	OTHER
Disorders involving intracorpuscular abnormalities				
Hereditary spherocytosis	During crises	Deserved by nearly all patients	Not indicated	
Nonhereditary spherocytosis	If severely anemic	Most cases if anemic	Not indicated	
Hereditary elliptocytosis	If severely anemic	If hemolytic anemia and splenomegaly develop	Not indicated	
Thalassemia major	During stress or severe anemia	For mechanical reasons or if transfused normal cells are destroyed rapidly	Not indicated	
Sickle cell anemia	During stress or severe anemia and to heal leg ulcers	Occasionally in childhood if anemia is severe	Not indicated	? priscoline for adbominal pain; avoid hypoxia
Sickle cell trait	Unnecessary	Not indicated	Not indicated	Avoid hypoxia
Sickle cell thalassemia	About the same as in sickle cell anemia	As in sickle cell anemia	Not indicated	Avoid hypoxia
SC, SD, or CC disease	During stress or severe anemia	Rarely indicated	Not indicated	Avoid hypoxia in SC, SD
Congenital nonspherocytic hemolytic anemias	During stress or severe anemia	Not indicated	Not indicated	
Porphyria erythropoietica	During stress or severe anemia	To relieve hemolytic anemia and photosensitivity	Not indicated	

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Paroxysmal nocturnal hemoglobinuria	During stress or severe anemia (washed cells)	All operative procedures to be avoided if possible	Not indicated	Iron in some cases; (?) dextran during crises
Disorders involving extracorpuscular abnormalities				
Autoimmune hemolytic disease	Only if anemia is severe or to prepare for surgery	In cases refractory to hormone therapy; response unpredictable	Indicated in nearly all cases; about 90 per cent are benefited	Treatment of underlying disease, if present
Leukemia, lymphoma, myeloma, carcinomatosis (*without demonstrable autoantibodies*) (intracorpuscular abnormalities may also be present)	During stress or severe anemia	If spleen is enlarged and transfusion requirement is excessive	Seldom affects hemolytic process, but may be indicated for other reasons	Treatment of underlying disease
Cirrhosis of liver, nephritis, other nonmalignant diseases	During stress or severe anemia	Only in some cases of congestive splenomegaly	Not indicated	Treatment of underlying disease
Idiopathic hypersplenism	During stress or severe anemia	If other diagnoses are excluded; especially if spleen is enlarged	Probably not indicated	Maintain suspicion of underlying disease

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of these cases, especially those with splenomegaly in which there may be marked deceleration of hemolysis after splenectomy. In some cases premature senescence of the red cells is thought to occur[2] and in others, especially myelocytic and monocytic leukemia and myeloid metaplasia, morphologic abnormalities of the red cells may be apparent. Comment on the presence of spherocytosis in these conditions has already been made. Hemolytic anemia accompanying malignant disease may thus be due to intra- or extracorpuscular abnormalities or to both. In our experience and in that of Wasserman and associates,[2] administration of ACTH or cortisone seldom affects the hemolytic process *in the absence of demonstrable autoantibodies.* Wintrobe,[44] on the other hand, has found cortisone useful in treatment of hemolytic anemia accompanying chronic lymphocytic leukemia and Hodgkin's disease. Further experience may reveal whether amelioration of hemolysis in such cases is due to a "direct" effect of steroid on the hemolytic process or to an indirect effect resulting from improvement in the underlying disease.

Splenectomy may be indicated if the spleen is enlarged and if normal transfused red cells are found to be destroyed rapidly. For example, one of our recently observed patients with chronic lymphocytic leukemia required transfusion of 500 ml. of sedimented red cells every 10 days in order to maintain the volume of packed red cells at 15 to 17 per cent. During the 8 months that have now passed since removal of an enlarged spleen, no transfusions have been needed and the packed red cell volume has remained above 40 per cent. No autoantibodies or irregular isoantibodies were demonstrable in this case. The patient's red cells were normal in size, shape, and osmotic fragility. Hyperbilirubinemia was never present despite marked shortening of survival of transfused red cells, as measured with radioactive chromium prior to splenectomy. There was no evidence of blood loss.

Hemolytic Anemia Associated With Other Diseases.—Hemolytic anemia may be encountered as a complication of certain chronic nonmalignant diseases, such as cirrhosis of the liver and chronic nephritis, and without demonstrable autoantibodies or noteworthy morphologic abnormalities of the red cells. Signs of hemolysis and increased bile pigment production are usually minimal, as in a large share of the cases referred to in the preceeding paragraph. Wasserman and associates,[2] apply the term "hemopathic hemolytic anemia" to such cases. Therapy should be directed toward correction of the underlying disease if possible. Transfusion of normal red cells may be needed, but splenectomy is seldom indicated except in some cases of congestive splenomegaly associated with cirrhosis of the liver. Use of ACTH or cortisone appears to be of no value in most instances.

Idiopathic Hypersplenism.—Hemolytic anemia due to primary or idiopathic hypersplenism is a rarity, that is, if this term is applied only to cases in which there is no evidence of autoimmunization, of underlying disease such as lymphoma or leukemia, or of abnormalities in shape or osmotic fragility of the red cells. We have encountered only 2 such cases in the past 10 years. Both were middle-aged women with chronic normocytic anemia, reticulocytosis, normoblastic hyperplasia of the bone marrow, slight hyperbilirubinemia, and spleno-

megaly. Anemia was promptly relieved by splenectomy in both cases and has not recurred during 10 years of observation in one case and 6 years in the other. Sections of the spleens showed no distinctive abnormalities.

In our experience, patients in whom idiopathic hypersplenism was suspected usually proved ultimately to be suffering from autoimmunization, lymphoma or granulomatosis, or atypical hemolytic anemia with intracorpuscular abnormality of the red cells. Under the circumstances described in the preceding paragraph splenectomy is indicated. We have had no experience with administration of ACTH or cortisone in such cases.

Miscellaneous.—No attempt is made in this paper to comment on treatment of all known types of hemolytic disorders. In particular, discussion is omitted on the relatively acute hemolytic processes such as encountered after severe thermal burns, exposure to or ingestion of chemicals and drugs, in favism, in hemolytic disease of the newborn, and after transfusion of incompatible red cells or plasma. Discussion of pernicious anemia is also omitted despite the fact that the red cells in this disease have been shown to have shortened life span[45,46] when transfused to normal recipients. Hamilton and associates[47] have also demonstrated shortened survival of normal red cells in patients with pernicious anemia transfused prior to administration of vitamin B_{12}.

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SUMMARY

Therapy currently recommended for the hemolytic disorders discussed in this paper is summarized in Table I.

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THE TREATMENT OF REFRACTORY ANEMIA OR BONE MARROW FAILURE

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THE treatment of patients with hypoplastic anemia is usually unsatisfactory and discouraging. Painstaking care, however, regularly makes patients more comfortable, often prolongs productive life for months or years, and occasionally is rewarded by a remission. Even though specific agents for stimulating an aplastic marrow are not yet available, the ability to determine the approximate relative importance of decreased cellular formation and accelerated breakdown in any given case makes a more physiologic approach to therapy possible, particularly with respect to splenectomy. The importance of persistence is indelibly impressed on physicians who treat many such cases by experiences like the following: A young man, followed by the medical service at Barnes Hospital, had manifestations of aplastic anemia for 5 years; after nearly 600 transfusions, corticoid therapy, and splenectomy, he developed an apparently complete remission which has now lasted for 6½ years.

While a description of the various manifestations of hypoplastic anemia is not appropriate in this discussion of therapy, a few statements about definition, etiology, and differential diagnosis should be made.

GENERAL CONSIDERATIONS

Definition.—Hypoplastic anemia has been variously designated as refractory anemia, aplastic anemia, aregeneratory anemia, and by a number of other names. It can best be regarded as bone marrow failure. All marrow elements may be involved, in which case pancytopenia is found in the peripheral blood, or there may be failure of only one or two of the cell types to give anemia without leukopenia and thrombocytopenia, anemia and leukopenia without thrombocytopenia, etc. A rough comparison may be made with cardiac failure where manifestations may be primarily those of insufficiency of the right ventricle, the left ventricle, or both.

The term refractory anemia[1] has the advantage of indicating that the process does not usually respond to available therapy without implying that the marrow is necessarily hypocellular. The marrow actually may be hypoplastic, normally cellular, hypercellular, or partially fibrotic. There often is immaturity of cells as

if a maturation arrest were present, and neutrophils are frequently deficient in granules. But even when the marrow is cellular, one cannot at present determine, except for erythrocytes, its functional capacity; the peripheral pancytopenia may be due to a maturation arrest in the marrow, to a failure of delivery of the cells to the peripheral blood, or to peripheral destruction of cells being manufactured at normal or greater than normal rates. In the author's laboratory, the experimental production of bone marrow aplasia has been studied in dogs given large doses of estrogens and in several species of animals given aminopterin.[2] In both series of experiments, the marrow often seemed to become hyperplastic, then progressively less cellular until frank aplasia had been produced. It is tempting to believe that the different types of marrow morphology observed in patients with refractory anemia may represent different stages in essentially the same pathologic process.

Etiology and Pathogenesis.—Refractory anemia may be idiopathic or it may follow exposure to chemical agents and ionizing radiation. Benzol, organic arsenicals, gold compounds, nitrogen mustard, folic acid antagonists, Atabrine, dinitrophenol, trinitrotoluene, hair dyes, volatile insecticides (Lindane), chlorophenothane (DDT), anticonvulsant drugs (Tridione, Mesantoin), streptomycin, chloramphenicol, chlorpromazine, Tapazole, and Pyribenzamine have all been reported to cause aplastic anemia. While an immune mechanism has not been demonstrated and a direct toxic effect on the bone marrow is probably exerted, there is a striking difference in the susceptibility of different persons to most of these substances. Irradiation exposure of sufficient magnitude to cause pancytopenia is encountered only in people who receive large doses of irradiation therapeutically, through industrial accidents, or at the time of nuclear explosions. Accidental industrial exposure will probably become more frequent as atomic energy power plants become more common. The chemical changes produced in cells by ionizing irradiation are not completely understood, but the synthesis of desoxyribosenucleic acid by the nucleus seems to be inhibited and mitosis becomes arrested. Animals exposed to lethal doses of irradiation have a higher recovery rate if a portion of their tissues, as for instance the spleen, is shielded during the exposure.[3] Presumably, protected reticuloendothelial cells may reseed the marrow and form active hematopoietic tissue.

Rare cases of hypoplastic anemia are observed as congenital disorders characterized either by pancytopenia (Fanconi syndrome) or by pure red cell aplasia alone. There has recently been considerable interest in the association of refractory anemia with thymic tumors.[4,5] In a few instances, autoantibodies to all blood elements have been thought to be responsible for the development of pancytopenia.[6] The spleen does not appear to be directly involved in the pathogenesis of hypoplastic anemia, but as patients are treated with transfusions and develop transfusion hemosiderosis, the spleen may enlarge and aggravate the effect of the hypoplasia either by increasing destruction of peripheral cellular elements or possibly by exerting an inhibitory effect on the marrow.

In many patients, however, no etiologic factor whatever is discernible, and the marrow failure must be regarded as idiopathic.

Differential Diagnosis.—The diseases most likely to be confused with hypoplastic anemia are subleukemic leukemia and other forms of myelophthisic anemia. Differentiation must be made largely on the basis of bone marrow examination, although the presence of lymph node and splenic enlargement is also helpful. The problem is made more difficult by the fact that some cases will appear for weeks or months to be examples of marrow aplasia only to develop later the morphologic changes of leukemia. If marrow aspiration yields a "dry tap" or is otherwise unsatisfactory, surgical trephine of the marrow cavity to obtain an adequate specimen must always be done.

THERAPY

The therapeutic management of patients with hypoplastic anemia can best be treated under the following headings: (1) recognition and removal of the cause if possible; (2) use of transfusions and other supportive measures; (3) treatment of infections and hemorrhagic manifestations; (4) attempts to stimulate marrow function; and (5) consideration of splenectomy.

Recognition and Removal of Cause.—In a few patients, the temporal relationship between exposure to ionizing irradiation or to a chemical marrow toxin and the development of hypoplastic anemia is immediately obvious, and further exposure can be avoided. In most instances, however, it is difficult to be sure that a chemical substance has actually caused the aplasia. One industrial worker exposed to benzol develops pancytopenia while his associates, similarly exposed, remain normal. If a man with marrow failure has used Lindane or DDT around his home, the insecticides must be held suspect. One recently observed patient illustrates the problem well.

An elderly woman, 84 years of age, had an elective cholecystectomy because of three recent attacks of gall-bladder colic. She otherwise had been well and her blood was normal. The operation was done without difficulty but she was treated postoperatively, as prophylaxis against infection, with six intramuscular injections of chloramphenicol, 1 Gm. each, at intervals of 8 hours. Eight weeks later she began to feel tired. After an additional two weeks, she noticed ecchymoses and petechiae. She was then found to have an anemia of 10 Gm., 2,000 white blood cells per cubic millimeter with very few granulocytes, very few platelets, and a fatty, hypocellular marrow.

There is no known test that can be applied to prove that the 6 Gm. of chloramphenicol had caused the marrow aplasia. One would have to wait until the patient recovered, if indeed she ever does, and readminister the drug to see whether the hypoplastic anemia would recur. Such an observation is obviously too hazardous to make; the result, furthermore, would be conclusive only if the disease were reproduced. Under these circumstances, one is forced to advise that further contact be avoided with any substance which might reasonably be expected to cause marrow damage. The patient should be advised against the further use of hair dyes, insecticides, plant sprays, volatile solvents, and all drugs except those specifically prescribed. It is even worth while for the physician to visit the patient's home and place of business so that he can scout around on his own in search of offending agents which may have escaped the attention of the patient. In one instance known to the author, a physician's two sons developed

aplastic anemia. The father, while making a thorough search of his home, found a container of Paris green in the garage which he had not known was there and in which the boys had been playing.

There remain, however, many patients in whom no marrow toxin can be identified. Prognosis is definitely better when exposure to a toxin can be identified and eliminated, although the mortality rate remains high.

Approximately 15 patients with benign thymoma and refractory anemia have now been described. In most instances, the marrow hypoplasia has been limited to erythrocytic tissue, but in some cases it has been generalized. Thymectomy has been associated with marked improvement or cure in four cases but has failed to alter the course of the disease in other instances.[4,5]

Transfusions and Supportive Care.—Transfusions constitute the backbone of any program for the treatment of refractory anemia. Because they may have to be given for a long time, special precautions must be taken to avoid later difficulty.

a. Every venipuncture must be done with great care to minimize trauma to veins. After the needle is withdrawn, pressure at the venipuncture site must be maintained longer than usual to avoid hemorrhage into the tissues. These are small points, but their importance is painfully obvious if all usable superficial veins have been ruined, and blood must be transfused into the femoral vein.

b. Blood typing of both the patient and the donors should include the Rh factors and whatever other minor blood groups the laboratory is prepared to identify. The blood transfused should be as type-specific as possible to avoid sensitization to minor blood groups. All crossmatches should be checked with an indirect Coomb's test performed on the donor's red cells and the patient's plasma.[7] Incompatibilities not otherwise discernible can be detected in this manner.

c. Because of the decrease in cell viability with storage, blood should be transfused within the first 5 days after it has been collected in acid citrate dextrose solution.

d. Unless transfusions are being given to combat shock and hemorrhage, they should be administered only when the hemoglobin level has dipped below 9 Gm. per 100 c.c. If a patient has 8.5 to 9 Gm. of hemoglobin, he can be given two or three 500 c.c. units of blood on successive days and be free of the need to receive blood until his hemoglobin drops below 9 Gm. again—often an interval of 3 or more weeks. In this way his blood values are kept high enough so that he is comfortable, yet the minimum number of transfusions is given. The inevitable development of transfusion hemosiderosis and of sensitization to minor blood groups is thereby postponed as long as possible.

In spite of all precautions, after 50 or more transfusions, the frequency of reactions gradually increases. It has recently been demonstrated that some, perhaps the major portion, of these reactions result from acquired sensitivity to transfused leukocytes and platelets; to a large degree they can be prevented by removal of the buffy coat from the blood to be transfused.[8]

Other supportive measures should include an adequate diet with maintenance of a good nutritional status. No value is derived, however, from excessively high protein intakes, large amounts of liver, or similar special diets. As

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much as possible, the patient should be permitted to live a normal life, working at his usual occupation if he can do so without undue fatigue.

Treatment of Infections and Hemorrhagic Manifestations.—Prognosis in terms of relatively long survival is definitely better in those patients who have only mild degrees of neutropenia and thrombocytopenia. Death occurs in hypoplastic anemia from infection or hemorrhage, not as a rule from anemia. The prevention and treatment of these two complications, therefore, is of prime importance.

The prophylactic use of broad-spectrum antibiotics is unsatisfactory and hazardous because this will allow infection to develop from antibiotic-resistant bacteria and from mycotic organisms.[9,10] The mouth should be kept clean, but dental manipulations should be limited to the minimum necessary, catheterizations should be avoided, and constipation with its resultant trauma to the rectal mucosa and anus should be prevented. If the neutropenia is severe, it is better to avoid contacts with crowds of people or with individuals with known upper respiratory infections. When an infection of any kind does occur, antibiotic therapy should be instituted promptly. Often it is important to begin therapy before the infectious agent can be identified. For instance, if pneumonia develops in a patient with aplastic anemia, we prefer to take sputum and blood cultures, then provide broad coverage promptly with penicillin and Achromycin. When the results of the cultures are known, therapy is altered accordingly.

Hemorrhagic manifestations are almost invariably due to thrombocytopenia. Corticoid therapy increases capillary resistance and frequently diminishes bleeding abnormalities even though the platelet count remains unaltered.[11] We prefer to give such patients prednisone, 5 mg. every 6 hours, increasing the dose if necessary, then gradually decreasing it until the minimum effective level is attained. In our experience, hemorrhagic manifestations not controlled by 50 mg. prednisone per day are seldom benefited by larger doses. The same precautions usually employed with corticoid therapy should be observed: low salt intake if fluid retention occurs, careful attention to the possibility of potassium loss, prophylactic coverage with isoniazid if there is reasonable suspicion of pulmonary tuberculosis, and occasional urinalyses to detect glycosuria.

On rare occasions, when bleeding is severe, platelet transfusions may be tried. These can most simply be done with plastic transfusion bags containing sequestrene as the anticoagulant; special sets of this type are now commercially available from manufacturers of plastic transfusion equipment. The donor is carefully cross-matched with the patient beforehand so that his blood may be administered immediately after collection. The patient's platelet count can be raised in this manner to levels high enough to stop oozing unless the patient has been sensitized to platelets by previous transfusions. In an unsensitized individual, the transfused platelets disappear from the circulation over a period of 6 to 12 days.

Very rarely bleeding from the uterus may be so persistent and extensive as to justify hysterectomy. The operation in a severely thrombocytopenic woman is extremely hazardous and should be done only as a desperation measure.

All medications, if possible, should be given by mouth. Subcutaneous and intramuscular injections cause hematomas which are painful and subject to

abscess formation. Intravenous injections risk damage to veins sorely needed for the transfusions.

Attempts to Stimulate Marrow Function.—The ideal therapy would, of course, be a stimulating agent which could correct the marrow failure and return its function to normal. Vitamin B_{12}, folic acid, other B vitamins, and crude liver extract are all without effect. Adrenocorticotropic hormone or other corticoid preparations and cobalt are also usually of no therapeutic value, but an occasional patient is benefited.

The author and his associates have now seen 5 patients with refractory anemia who had a reticulocyte response and the return of normoblastic marrow activity after administration of ACTH, cortisone, or prednisone.[12] The effect on erythropoietic tissue seemed greater than on leukocytes and platelets and was usually not sustained until after splenectomy (vide infra). Similar patients have been observed by other hematologists, sometimes apparently with an effect on white cells and platelets, too. It is emphasized that this type of result is the exception rather than the rule. Even so, it seems definitely worth while to try the effectiveness of corticoid therapy in most individuals with refractory anemia, following the peripheral blood and bone marrow for a period of two weeks. If definite improvement has not occurred during that time, the therapy should be discontinued unless it is needed to help control bleeding manifestations.

Similarly, there are five reports of favorable responses to the administration of cobalt, as 100 to 180 mg. of cobaltous chloride per day.[13] Most patients fail to respond. The author has never observed a good therapeutic effect in any of his patients, but there seems little reason to question the results in the five instances referred to previously. For this reason, a trial of cobalt for 2 or 3 weeks seems justified.

With the recent interest in the erythropoietic hormone, there seemed reason to hope that this substance, if ever available in concentrated form, might have considerable effectiveness. Cobalt seems to induce an increased production of the erythropoietic hormone.[14] If cobalt exerts its stimulating effect on erythropoiesis through such a mechanism, there is little reason to think that the erythropoietic hormone would be any more effective than cobalt itself.

When marrow failure is secondary to arsenic intoxication, BAL should be tried. BAL is not, of course, a stimulating agent but it might be effective in releasing the marrow from the depressive activity of the arsenic.

Consideration of Splenectomy.—Splenectomy would be of value under two circumstances: (a) when the spleen is enlarged and is destroying cells at an accelerated rate; or (b) if a malfunctioning spleen were depressing marrow function.

An accelerated rate of cellular destruction by the spleen can be demonstrated with currently available methods only for red cells. If a transfusion is required oftener than once every 10 days in order to maintain the red cell count at a given level, and the patient is not bleeding, one can assume an increased rate of hemolysis. This statement is derived from the following simple calculation. The normal survival time for red cells in the circulation is 120 days. A patient with a blood volume of 5,000 c.c. has roughly 10 pints of blood. He destroys, with a normal

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corpuscular survival time, the red cells in one pint of blood about every 12 days (120 divided by 10). With a blood volume of 4,000 c.c., the value would be 15 days. Therefore, it is conservative to estimate that a transfusion requirement greater than 1 pint in a 10-day period indicates accelerated cellular destruction. More direct measurement of hemolysis can be obtained by tagging the patient's own erythrocytes with radioactive chromium and reinjecting the cells. Normal half-time survival of these tagged cells is about 30 ± 3 days; a shorter half time signifies increased hemolysis. In order to determine that the spleen is responsible for the accelerated destruction, one can measure the selective uptake of the radioactive chromium by surface counting over the spleen. If the activity over the spleen is several times greater than that over the liver, one is justified in assuming that the spleen is at least partially responsible for the increased hemolysis.[15] Splenectomy in such patients is often followed by a decreased transfusion requirement, and occasionally the red cell count will even equilibrate at a level high enough to make further transfusions unnecessary. Much of the "black eye" which splenectomy has received in the treatment of hypoplastic anemia is due to the fact that it is done indiscriminately without first establishing that there is a hemolytic component to the anemia, and then trying to determine how important a role the spleen plays in the hemolytic process. One other point deserves emphasis. A patient in the early stage of this disease may have a normal-sized spleen and a normal red cell survival time; as he develops transfusion hemosiderosis the spleen enlarges and may then become the site of increased red cell destruction. The fact, therefore, that hemolysis may be of no importance early in the disease does not eliminate the possibility that it may become so later.

Any depressive effect of an abnormal spleen on the marrow is much more difficult to demonstrate or to be sure about. In two of our patients with pure red cell hypoplasia, splenectomy was followed by a reticulocytosis (in one case to 21 per cent), normoblastic hyperplasia in the marrow, and a rise in red cell values.[12] These are isolated experiences, but it is difficult to explain them in any way other than by a depressive effect of the spleen on the marrow.

In summary, we feel that splenectomy in hypoplastic anemia should be reserved for those patients in whom a hemolytic component to the anemia can be demonstrated. If isotopic techniques are available, one should also attempt to demonstrate that the spleen is an important site of the accelerated destruction. It is our impression that those patients who respond to corticoid therapy with a reticulocytosis tend to respond to splenectomy particularly well.[12] If splenectomy is limited to those patients who have increased hemolysis, the results in terms of diminished transfusion requirements and an occasional remission are rewarding. The procedure should not be done indiscriminately.

CONCLUDING COMMENTS

It is evident from what has been said that only a minority of patients with hypoplastic anemia recover. Remission rates are somewhat higher for those patients in whom an exogenous marrow toxin can be identified and eliminated. Among the remaining patients, the longest survivals tend to occur when leukopenia and thrombocytopenia are mild rather than severe. Diligent and persistent

therapeutic management is always important because remissions may occur after the disease has been present for years. Even those patients who do not recover can be made much more comfortable and can often be kept productive. One's efforts should be directed at helping them to live as normal a life as possible. Transfusions should be given whenever possible on an outpatient basis, spaced for the convenience of the patient as well as of the physician. Careful attention to details of supportive care and judicious use of the few therapeutic agents available can make the difference between a miserable existence and a relatively happy few years of life.

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THE TREATMENT OF POLYCYTHEMIA VERA

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POLYCYTHEMIA vera is a chronic disease of unknown etiology, the chief clinical manifestations of which are headaches, fatigability, dizziness, pruritus, splenomegaly, plethora, cyanosis, and systolic hypertension. Elevations of the erythrocyte level, the hemoglobin concentration, and the hematocrit value constitute the most consistent laboratory findings, but in the majority of cases the leukocyte count and the thrombocyte level are also elevated, occasionally strikingly so, which suggests that all of the principal cellular elements of the bone marrow participate in the hyperplastic process. From the standpoint of therapy, it is important to keep in mind that most of the clinical manifestations as well as one of the most feared complications of polycythemia vera (intravascular thrombosis) can be attributed directly or indirectly to three factors, (1) the increased total blood volume, (2) the increased viscosity of the blood, and (3) the thrombocytosis. Until the etiology of this disease is elucidated, the goal of therapy must be to relieve the symptoms of the disease, to minimize the danger of intravascular thrombosis, and to avoid, in so far as is possible, any procedure which significantly increases the incidence of, or hastens the appearance of, such dreaded complications as leukemia, leukemoid reactions, and myelofibrosis.

The rapidity with which the feeling of fullness and aching in the head, the dizziness, and the fatigability characteristic of polycythemia vera can be relieved by repeated phlebotomies alone has contributed to the general belief that the increased blood volume is a major factor in the pathogenesis of these symptoms. Some patients with this disease will continue to have mild symptoms at times when the erythrocyte level and the hematocrit value are in the upper portion of the normal range and yet will be completely asymptomatic when these values are reduced to the lower normal range. The extent to which increased viscosity of the blood contributes to the symptoms and to the high incidence of intravascular thrombosis in this disease is also not entirely clear; but it is known that the circulation time may be greatly prolonged in polycythemia vera with resultant visceral stasis, and it is apparent that increased blood viscosity is at least a contributory factor in this phenomenon. Studies by several investigators[1,2] indicate that there is a linear relationship between the hematocrit level and

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blood viscosity up to hematocrit values of approximately 60 per cent, above which the viscosity increases more rapidly than would be predicted by such a linear relationship. Others,[3,4] although unable to confirm a linear relationship between hematocrit and blood viscosity at hematocrit levels within the normal range, also noted an accelerated rate of increase of viscosity at abnormally high hematocrit values. Lawrence[5] measured the blood viscosity in 55 polycythemia patients having red blood cell counts ranging from less than 4 to more than 11 million per cubic millimeter and found a coefficient of correlation of 0.55 between these values. Bircher[6] states that the relationship between viscosity and red blood cell concentration is hyperbolic. These findings suggest that with increasing hematocrit levels above 60 per cent, a prompt reduction in hematocrit becomes increasingly imperative to minimize the danger of thrombosis.

The total blood volume can be lowered with a resultant decrease in blood viscosity by removal of blood (venesection, induced hookworm infestation), by hemolysis (phenylhydrazine), by suppression of excessive cellular multiplication in the bone marrow (x-ray therapy, radioactive phosphorus, nitrogen mustard, or one of its derivatives, Fowler's solution), or by inducing an iron deficiency state.

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REMOVAL OF BLOOD

Venesection is the quickest method of achieving this goal. When an elderly patient with significant arteriosclerosis, a very high hematocrit value, and marked thrombocytosis is seen for the first time, prompt and repeated phlebotomies are definitely indicated. This procedure alone will not lower the thrombocyte level, and it has even been claimed[7] that repeated blood withdrawal results in secondary marrow stimulation. There can be little doubt but that chronic hemorrhage in a normal individual may produce reticulocytosis, leukocytosis, and thrombocytosis, but that this occurs in polycythemic patients treated with venesection has not been proved.[8] At any rate, the lowering of the blood viscosity will probably more than offset the effect of any slight rise in thrombocyte level. This procedure should then be followed by some form of therapy designed to suppress marrow cellular activity. In young patients with minimal or no vascular disease and in patients with mild polycythemia with an hematocrit value below 60 per cent and no thrombocytosis, it may be worth while to attempt to control the disease by phlebotomies alone. If the withdrawal of 500 to 1,000 c.c. of blood once every 3 to 4 months completely controls the clinical manifestations and the hematocrit level, marrow suppressive forms of therapy may logically be withheld until the patient is older or the disease more active. The disadvantages of venesection alone are that it not only fails to restore the platelet and leukocyte levels to normal (when elevated), but it also results in less even control of the erythrocyte level and of the symptoms; it necessitates more frequent visits of the patient to the physician; it is somewhat unpleasant to the patient, and an iron deficiency state with hypochromia of the erythrocytes invariably develops sooner or later and may result in significant symptoms.

Artificially induced hookworm infestation has been advocated by several observers[9,10] as a means of inducing continuous low-grade blood loss for the purpose of achieving more even control of the hematocrit level and viscosity

than can be obtained by venesection. The technical difficulties encountered in regulating the rate of blood loss, and the psychologic disadvantages can be expected to prevent widespread use of this method.

INDUCED HEMOLYSIS

Some years ago phenylhydrazine enjoyed great popularity in the treatment of polycythemia vera. This drug is a potent hemolytic agent; there can be no doubt but that it will lower the red blood cell count, the hemoglobin concentration, and hematocrit level if given in sufficient dosage. The drug produces a delayed hemolytic effect and if given in large doses may result in jaundice and severe anemia. It is probably wise to lower the blood volume first by phlebotomies, and then give interrupted short courses of phenylhydrazine to maintain the normal state rather than to attempt to lower the hematocrit from very high values by administration of this hemolytic agent alone. The recommended dosage for this purpose is 0.1 Gm. daily or every other day for a total of 10 doses. Such a course of treatment may be repeated after an interval of 10 days as often as necessary to maintain adequate control of the blood. When given in this fashion the drug would appear to be quite safe.

Phenylhydrazine has been shown to produce liver damage when given in very large doses to dogs,[11] but such an effect has not been reported with the much smaller doses employed for human therapy. Phenylhydrazine may lower the platelet level apparently due to a direct lytic effect; this is desirable in one sense, but it has been suggested that the breakdown of thrombocytes may increase the hazard of intravascular thrombosis. For this reason, the drug should not be given to elderly patients, to anyone with significant arteriosclerosis, or during a postoperative period.

Phenylhydrazine is not as effective or easy to use as certain other more modern methods of therapy, but it probably still has a place in the management of those patients with polycythemia vera who no longer respond to safe doses of P^{32} and whose available veins have been thrombosed by repeated venesections. It may also be of use in the management of patients with thrombocytopenia in whom the use of agents causing inhibition of bone marrow activity is contraindicated.

SUPPRESSION OF BONE MARROW ACTIVITY

Low Iron Diets.—When blood is repeatedly withdrawn from a patient with polycythemia vera, the erythrocytes become progressively smaller and more hypochromic, and an iron deficiency develops. The iron deficiency state then has a suppressive effect on erythropoiesis in the bone marrow. That this is so is clearly demonstrated by the fact that when iron is administered under these circumstances, a reticulocytosis and rapid rise in the erythrocyte level may ensue. Such observations have led to attempts to control the excessive production of erythrocytes in this disease by deliberately producing an iron deficiency state by means of a diet low in iron supplemented by occasional phlebotomies as needed.

A few observers consider that phlebotomy, with the production of iron deficiency, is the treatment of choice at the present time. Dameshek[12] advocates

the following program of management. The red cell mass is first reduced by venesections of 500 c.c. each twice weekly until the hematocrit has reached about 45 per cent; from 2 to 4 weeks are usually required. At this time a low iron diet is instituted to facilitate development of chronic iron deficiency; the patient is instructed to limit very strictly his intake of red meat, liver, eggs, shellfish, brown cereals, and certain vegetables high in iron content; adequate protein intake is assured by consumption of 2 to 4 glasses of milk daily plus fish, fowl, and lamb or veal twice weekly. According to Dameshek there is usually a gradual rise in red cell count beginning 2 or 3 months after the completion of the phlebotomies, but hemoglobin and hematocrit remain low and symptoms reduced or absent for 3 to 18 months, after which venesections are once again necessary to return the hemoglobin and hematocrit levels to normal. Dameshek notes the persistence of thrombocytosis, leukocytosis, and splenomegaly on this regimen and states that glossitis may develop in patients so treated.

The chief disadvantages of this program of therapy are that iron has important functions in the body other than in erythropoiesis (it is present in myoglobin, cytochrome, catalase, and peroxidase), and patients suffering from sufficient iron deficiency to be effective in controlling polycythemia usually feel tired. The general lack of feeling of well-being may be so marked that only the most enthusiastic physician can persuade the patient to adhere to the diet over a period of many years.

Benzol.—One of the earliest chemotherapeutic agents used in an attempt to suppress the excessive cellular multiplication in the bone marrow in polycythemia vera as well as in leukemia was benzol.[13] The toxic effects of this cellular poison were so great that it is no longer used. Potassium arsenite in the form of Fowler's solution was also used in the treatment of chronic myelocytic leukemia and polycythemia vera,[14] but here again control of the disease proved to be erratic and the toxic effects were formidable. Other more effective means of suppressive therapy are now available.

Nitrogen Mustard.—Nitrogen mustard has now had an extensive trial in the therapy of polycythemia vera. Spurr and associates[15] treated 10 patients with a standard dose of 0.4 mg. of nitrogen mustard (methyl-bis, β-chloroethylamine hydrochloride) per kilogram body weight; there was an average fall of 25 per cent in erythrocyte level, the maximum effect being reached in 4.4 weeks (average).

Woodruff[16] noted no satisfactory clinical or hematologic response following 0.9 mg. per kilogram dose of nitrogen mustard given over a period of 64 days, while Wilkinson and Fletcher[17] obtained significant subjective and objective improvement in only one of 3 cases treated with conventional doses of this agent.

The chief disadvantages of nitrogen mustard therapy are that the beneficial therapeutic effects are not consistent and are of relatively brief duration, necessitating frequent unpleasant re-treatment.

Triethylene Melamine.—Triethylene melamine has also been reported to produce temporary beneficial effects.[18,19] Rosenthal and Rosenthal[18] studied the effects of this agent in 30 patients, utilizing administration of 2.5 to 5.0 mg. triethylene melamine every 1 to 3 days. A satisfactory response was obtained

in 20 of these with total doses of from 15 to 40 mg., while total dosage up to 65 mg. produced partial remission or no response in the remaining 10 patients. The better responses were generally found in younger patients and in those with short duration of disease and exhibiting more nearly normal white cell and platelet counts. Ellison, Ginsberg, and Watson[19] treated 6 patients with triethylene melamine, administering 5.0 mg. daily for 4 days as a single course of therapy. This dosage was repeated in 4 weeks if no significant response had occurred. Hematologic improvement as indicated by a significant fall in the hematocrit was noted in all 6 cases. Five of the patients had symptoms attributable to this disease; 3 of these had complete relief following therapy, and the other 2 had a decrease in symptoms. Severe nausea and vomiting occurred in one patient. Hamerman and Melamed[20] noted a very rapid increase in erythropoiesis following a satisfactory response to this drug in one patient. Wasserman[40] treated 35 cases with TEM and reported short duration of remission, wide variation in dosage necessary to produce a satisfactory response, and poor response to subsequent courses of TEM following one remission obtained with this agent.

As additional compounds related to nitrogen mustard are demonstrated to have cancerolytic and myelosuppressive properties and become available, they will undoubtedly be given a clinical trial in the treatment of polycythemia vera. None of these newer mustard derivatives has as yet received sufficient clinical trial to permit evaluation.

Daraprim.—Isaacs[21] has reported favorable results following treatment with the antimalarial drug Daraprim (pyrimethamine), but there have been no confirmatory reports, and his own data do not indicate that the therapy is superior to more established methods of treatment.

Radiation Therapy.—Radiation therapy has been successfully employed in the treatment of polycythemia vera ever since Lüdin first reported the results of radiation of the bones.[22] Pack and Craver[23] outlined methods of administering such therapy in detail. Various other methods of administering x-ray therapy, radium, and thorium-X have been recommended,[24,25] but all of these have now been largely discarded in favor of total body ("spray") radiation[26] or radioactive phosphorus administration which will be discussed in detail later. Radioactive phosphorus therapy has certain advantages over x-ray treatment, but it should be emphasized that general body spray radiation properly administered by a radiologist who is experienced in the use of this method of treatment is very effective.

The effects of radiation therapy of any sort on the bone marrow are somewhat delayed, and it may be several weeks before the peripheral leukocyte count and thrombocyte level reflect the decreased rate of production of these cellular elements by their precursors in the bone marrow. Furthermore, several months are required before the erythrocyte count decreases to its ultimate lower level, due to the much longer life span of these cells in the peripheral circulation. Thus, it is usually desirable to lower the erythrocyte count to something approaching normal first and follow this by general body spray radiation.

Radioactive Phosphorus.—Since the inital report on the treatment of polycythemia vera with radioactive phosphorus in 1940[27] this form of therapy has

been used very extensively.[28-43] The senior author has treated 279 patients with polycythemia vera with radioactive phosphorus during the last 15 years. There is general agreement that the hematocrit value and the blood volume should be restored to normal or near normal levels before giving P^{32}, particularly in older patients and those with marked thrombocytosis or unusually high hematocrit values. Most investigators then give from 3.5 to 5.0 mc. of radioactive phosphorus (in the form of sodium phosphate solution) by intravenous injection, depending on the weight of the patient and the severity of the disease. The P^{32} may be given by mouth; since approximately 75 per cent of the phosphorus is absorbed from the gastrointestinal tract, the dosage of the drug should be increased correspondingly. The intravenous route is preferred as there are no reactions and the effective dosage is then known more accurately. No additional treatment (other than phlebotomies if necessary) is given for at least 3, and preferably 4, months after which no further change in the concentration of erythrocytes in the peripheral blood will occur as a result of the initial treatment. If the hematocrit level remains above 50 or 55 per cent, a second injection of 2.0 to 3.5 mc. of P^{32} is given. In the authors' experience, about 50 per cent of patients will require this second injection; only about 10 per cent of patients will then need a third injection of from 1.0 to 3.0 mc. after a second interval of 3 to 4 months. Wiseman[7] has outlined more rigid criteria for calculating the exact dosage of P^{32} based on the initial erythrocyte count and the thrombocyte level. Such rigid rules for determining dosage may be necessary for the guidance of the inexperienced, but in view of the large number of variables involved, the proper dose for any given patient cannot be accurately calculated in advance.

Lawrence[37] on analyzing 139 patients with polycythemia vera treated with P^{32} found that the average "course" of treatment consists of 6.7 mc. often spread out over a period of 3 to 6 months; whereas, in Stroebel's[43] series of 241 cases the dosage required to control the disease ranged from 3 to 21 mc. with an average of 5.7 mc. for the cases without leukocytosis and 8.3 mc. for patients with leukocytosis, thrombocytosis, or immature myeloid cells in the peripheral blood.

Marked symptomatic improvement can be anticipated after completion of such a course of therapy. In the authors' experience[28] the major symptoms of polycythemia vera (fatigability, headaches, dizziness, aching pains in the extremities, itching, blurring of vision, and burning of the eyes with or without lacrimation) are totally or partially relieved in over 90 per cent of patients after adequate P^{32} therapy. The physical signs of this disease respond equally well to such treatment. Plethora was completely relieved in 96 per cent of patients, cyanosis in 93 per cent of cases, conjunctival redness and distended retinal venules cleared up in all cases, and the spleen and liver became no longer palpable in 68 per cent and 62 per cent, respectively, of patients having these findings. Systolic hypertension returned to normal in 36 per cent of cases and was partially relieved in another 36 per cent.

The duration of remissions induced by a single "course" of radioactive phosphorus therapy varies from 6 months to over 7 years in the author's experience. Other investigators have reported remissions lasting from 1 to 2 or more years.[37,43]

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Almost all investigators who have had extensive experience in the treatment of polycythemia vera with P^{32} feel that this is the treatment of choice in so far as ease of administration, freedom from immediate toxic effects, relief of symptoms, correction of abnormal physical signs, evenness of control of hematologic findings, and duration of remissions are concerned. Certainly there is no other form of therapy at present which permits the patients to lose as little time from work or make as few visits to the physician.

The "immediate" or early hematologic complications of radioactive phosphorus therapy were first emphasized by Hempelmann and colleagues.[44] If an excessive dose of P^{32} is given, leukopenia or thrombocytopenia, or both, may develop within a period of 3 to 5 weeks. Anemia may also develop, but this does not become manifest until 3 to 4 months after the treatment is given. The authors have had no significant complications of this sort during the last 12 years since a proper dosage and treatment interval schedule has been worked out. However, the fear has been repeatedly expressed in recent years that P^{32} therapy might cause the conversion of polycythemia vera into leukemia or myelofibrosis. As leukemia, leukemoid reactions, and myelofibrosis are known to occur as part of the natural evolution of this disease in the absence of any type of radiation therapy, it is difficult to evaluate this factor. It would seem to be worth while to review the evidence in considerable detail, as there can be little doubt but that P^{32} is the treatment of choice, unless such treatment is contraindicated because of the leukemogenic, cancerogenic, and other late deleterious effects of radiation.

There will not be space to review here the well-known leukemogenic and cancerogenic effects of x-radiation. Brues and co-workers[45] showed that in mice P^{32} has leukemogenic effects comparable with those produced by x-rays. P^{32} was leukemogenic whether given in single or repeated doses. The effect became more marked as the dose was increased until a saturation value was reached. Finkel[46] reported the development of a few osteogenic sarcomas in mice given P^{32}. However, in rats P^{32} readily produces osteogenic sarcomas and carcinomas but does not produce leukemias.[47]

Stroebel, Hall, and Pease[43] have reported a total of 22 deaths out of a group of 148 patients with polycythemia vera who were treated with P^{32} and on whom an adequate follow-up was available. Of these deaths, 5 (23 per cent) were due to leukemia; this included 4 cases of acute leukemia and one of chronic myelocytic leukemia.

From January, 1942, to Aug. 1, 1956, 279 patients with polycythemia vera have been treated with radioactive phosphorus at the Washington University School of Medicine and the Barnes Hospital; 98 of these patients continued under our care up to the present time, or until the time of death. In some instances, the patients lived hundreds of miles away and we saw them only once or twice a year or even less frequently, but the attending physicians sent reports on the symptoms, physical findings, and blood counts at more frequent intervals. Of the patients who died, many died at home in distant cities; but, if a post-mortem examination was done, a copy of the autopsy protocol was obtained. All of the microscopic sections of the post-mortem material were borrowed for review by our pathologists whenever possible. The following data are derived from this

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14-year study of these 98 patients with polycythemia vera, all of whom received radioactive phosphorus therapy. For the first 4 years of this study, all patients in whom the diagnosis of polycythemia vera was definitely established were treated with P^{32}, but for the last 10 years an attempt has been made to control the disease by phlebotomies alone in patients under the age of 40 years. Hence, there has been some selection in terms excluding the younger patients in this series, but this disease is rare under the age of 40 years.

TABLE I. SIXTEEN PATIENTS WITH POLYCYTHEMIA VERA WHOSE DEATHS WERE DUE TO NONHEMATOLOGIC CAUSES

	AGE AT ONSET OF SYMPTOMS	SEX	P^{32} TOTAL MILLICURIES	DURATION FROM FIRST SYMPTOMS TO DEATH		AUTOPSY	CAUSE OF DEATH
				YR.	MO.		
E.K.	61	F	4.2	4	–	No	Cerebral vascular accident, probably thrombosis
M.S.	30	F	3.6	1	5	No	Cerebral vascular accident, probably thrombosis
J.G.	50	M	13.0	4	8	No	Pulmonary embolus from phlebothrombosis, right leg
J.M.	62	M	12.1	5	–	No	Sudden death due to (?) coronary thrombosis
A.W.	48	M	7.5	4	3	Yes	Acute myocardial infarction due to thrombosis
C.R.	66	M	15.0	7	7	Yes	Probable cerebral vascular thrombosis (head not examined)
O.S.	55	F	14.4	8	6	No	Cardiac arrest in O.R. during dilatation and curettage
W.C.	61	M	10.1	8	9	Yes	Subdural hematoma, left (spontaneous)
H.L.	53	M	7.7	4	9	Yes	Cerebral hemorrhage following minor trauma
L.D.	72	F	28.1	7	6	No	Hemorrhage from duodenal ulcer, recurrent
R.D.	61	M	6.6	6	–	No	Probable hemorrhage from duodenal ulcer
G.P.	59	M	3.2	1	–	No	Probable rupture of aneurysm of thoracic aorta
M.G.	51	M	5.0	11	–	No	Suicide
M.T.	13	F	11.0	16	–	No	Tumor of liver (exploratory laparotomy—no biopsy) Also had hypertension and azotemia
H.R.	66	M	9.3	6	–	No	Cause unknown (progressive weakness, terminal delirium)
O.T.	63	M	19.5	7	6	No	Cause unknown (no information available)

Of these 98 patients with polycythemia vera, 16 have died of nonhematologic disorders. The causes of death are summarized in Table I. Six of these patients died of vascular accidents which were probably due to intravascular thrombosis; this is 37.5 per cent of the patients in this group. Two of the patients died of proved intracranial hemorrhage, 2 of the patients who were known to have had duodenal ulcers in the past died at home with a history of terminal hematemesis or melena, and one patient who had a known aneurysm of the thoracic

aorta died suddenly at home with symptoms compatible with rupture of the aneurysm. Thus, 5 patients, or 31.2 per cent of the group, died of hemorrhage. Of the remaining 5 patients, one had had severe arteriosclerotic heart disease for many years and died of sudden cardiac arrest on the operating table during a dilatation and curettage. Another of the patients had vascular disease manifested by hypertension and azotemia. These findings confirm the commonly accepted opinion that thrombosis and vascular disease are responsible for the death of many of these patients.

TABLE II. NINE PATIENTS WITH POLYCYTHEMIA VERA WHO DIED OF ACUTE LEUKEMIA

	AGE AT ONSET OF SYMPTOMS	SEX	P^{32} TOTAL MILLICURIES	DURATION FROM FIRST SYMPTOMS TO DEATH		AUTOPSY	CAUSE OF DEATH
				YR.	MO.		
T.L.	48	M (Negro)	17.4	4	—	No	Acute monocytic leukemia
G.L.	36	M	27.8	5	6	No	Acute monocytic leukemia
W.S.	29	M	7.9	23?	—	Yes	Acute monocytic leukemia
J.S.	55	M	32.8	12	—	Yes	Acute monocytic leukemia
L.P.	58	F	21.0	9	—	No	Acute monoblastic or myeloblastic leukemia
E.L.	63	F	3.4	4	5	No	Acute myelocytic leukemia
M.Y.	65	M	18.2	5	—	No	Early acute myelocytic leukemia (died of uremia)
T.N.	47	F	21.0	7	9	No	Acute myelocytic leukemia
J.G.	59	F	14.9	14	—	No	Acute myelocytic leukemia, or, possibly ?Myelocytic leukemoid reaction

Nine patients died of acute leukemia. The data on these patients are shown in Table II. There were 8 well-established cases of acute leukemia and one probable case of acute myelocytic leukemia in this group. Four of the patients had acute monocytic leukemia; one patient had an acute form of leukemia with a very hyperplastic marrow containing 23 per cent blast cells which were certainly not lymphoblasts, but could have been either monoblasts or myeloblasts; and the other 4 patients had acute myelocytic leukemia. The basic criterion for the diagnosis of acute leukemia was the finding of a hyperplastic marrow containing 20 per cent or more blast cells.

Information concerning these patients with acute leukemia is summarized in Table III. The 4 cases of acute monocytic leukemia and the 4 cases of acute myelocytic leukemia are analyzed separately; the one patient whose marrow contained primitive cells which could have been either monoblasts or myeloblasts is excluded from this table.

The next group of patients is difficult to discuss as it was impossible in some of these cases to state with certainty whether the final pathologic state should be classified as chronic myelocytic leukemia, myelofibrosis, myeloid metaplasia, myelocytic leukemoid reaction, or some combination of these. In view of the differences of opinion among both clinical hematologists and pathologists as to whether chronic myelocytic leukemia and myeloid metaplasia represent distinct disease entities, or different phases or manifestations of a common disease state, it seemed wise to attempt to present data as to the anatomic findings with a minimum of personal interpretation. There were 12 patients in this group who developed what may be called "chronic myelopathies." Ten of the patients have died (autopsies were performed on 7 of these), and 2 are still living.

The data on these patients are summarized in Table IV. It is felt that 5 had chronic myelocytic leukemia. In all of these patients the bone marrow was examined either at autopsy, or shortly before death by aspiration, and was found to be hyperplastic with an increase in immature myeloid forms. An autopsy was performed on 3 of these patients, and in each case there was leukemic infiltration in many organs characterized by a uniform cell population made up almost entirely of immature myeloid cells. Although we believe that these cases should properly be classified as chronic myelocytic leukemia, they are shown in the chart only as "probable leukemia" because we are aware that some hematologists and pathologists would classify all of these as myelocytic leukemoid reactions. The 2 patients who are still living (the last 2 patients in Table IV) have tremendously enlarged spleens; they both have considerable numbers of myelocytes and promyelocytes in their blood and in the bone marrow; but recent bone marrow aspirations have yielded what appeared to be hypoellular marrow from which we surmise that these patients probably have myelofibrosis and myeloid metaplasia rather than myelocytic leukemia.

TABLE III. EIGHT PATIENTS WHO DIED OF ACUTE LEUKEMIA

Monocytic (4)

All were male
One Negro, three Caucasians
Average total dose of P^{32}—21.5 mc.
Average duration of total illness—approx. 11 years

Myelocytic (4)

One male, three females
All Caucasians
Average total dose of P^{32}—14.4 mc.
Average duration of total illness—approx. 8 years

Four of the patients in this group had myelofibrosis proved at autopsy and another 3 (2 still living and one who has died but on whom no autopsy was done) probably had myelofibrosis. The 3 patients who are thought to have had myelofibrosis had very large spleens, and they all had what seemed to be dense, hypocellular marrow on recent aspiration attempts (or shortly before death for the patient who has died). The second patient in Table IV had a leukemic marrow,

but her spleen was very hard and filled most of the abdomen; it is certainly possible that she had patchy myelofibrosis and myeloid metaplasia in addition to leukemia.

Four of these patients had myeloid metaplasia proved at autopsy, and 3, including the 2 who are still living, are thought to have myeloid metaplasia.

It should be emphasized that as many as half a dozen pathologists have examined the autopsy slides on some of these patients and there has been some

TABLE IV. TWELVE PATIENTS WITH POLYCYTHEMIA VERA WHO DEVELOPED CHRONIC MYELOPATHIES (TEN DEAD, TWO LIVING)

	AGE AT ONSET OF SYMPTOMS	SEX	P^{32} TOTAL MILLICURIES	DURATION FROM FIRST SYMPTOMS TO DEATH		AUTOPSY	CHRONIC MYELOCYTIC LEUKEMIA	MYELOFIBROSIS	MYELOID METAPLASIA
				YR.	MO.				
S.K.	45	F	12.1	4	9	Yes	*Probable*	*No* myelofibrosis at autopsy	
I.M.	52	F	29.0	3	6	No	*Probable*	?	? Spleen 23 cm. below C.M. at death
C.E.R.	38	M	19.1	19	—	Yes	*Probable*	*Yes*	*No.* Spleen 26 cm. (leukemic infiltrate)
M.W.	57	F	23.3	10	—	Yes	*Probable*	*No.* Spleen 1,800 Gm. but no B.M. fibrosis	?
A.M.	71	F	13.6	4	5	No	*Probable*	?	? Spleen only 2 cm. below C.M.
W.S.	61	M	32.9	9	1	Yes		*No.* Spleen 2,000 Gm. but no B.M. fibrosis	*Yes.* Striking megakaryocytic hyperplasia
V.A.	51	M	10.9	11	—	Yes		*Yes.* Very marked	*Yes.* Very marked
A.C.	66	M	3.8	3	2	Yes		*Yes.* Very marked	*Yes.* Moderate. Spleen 8 cm.
L.D.	26	F	19.6	24	—	No		*Probable*	*Probable.* Spleen 20 cm.
C.R.	66	M	15.0	7	—	Yes		*Yes.* Very marked	*Yes.* Very marked. Spleen 1,800 Gm.
V.T.	39	F	20.7	to Aug. 17 '56	2	—	?	*Probable.* Spleen extends into pelvis	*Probable*
K.H.	45	F	42.3	to Aug. 17 '56	—	—	?	*Probable.* Spleen 16 cm. below C.M.	*Probable*
				TOTALS			5 Cases	7 Cases	7 Cases

disagreement as to whether several of these patients had myelocytic leukemia or myeloid metaplasia. This difference of opinion might be interpreted by some individuals as evidence in support of the common pathogenesis and essential

identity of these pathologic states, but we have attempted to classify the cases for purposes of discussion into the most likely category considering both the blood and bone morrow data and the pathologic findings.

Of the 12 patients who developed chronic myelopathies, 5 were men and 7 were women. All were Caucasian. Most of these patients had had polycythemia vera for a relatively long period of time and had received fairly substantial amounts of P^{32}. The average total dose was 17.9 mc. There was no significant correlation, however, between either duration of illness (average, 10 years) or total dose of radioactive phosphorus and the type of chronic meylopathy which developed.

An additional 7 patients in this series of 98 cases of polycythemia vera have developed marked splenomegaly. All of them are still living and all have spleens which extend 9 to 20 cm. below the left costal margin in the midclavicular line. The most recent total leukocyte counts on these patients range from 4,900 to 60,000. Only 3 now have immature myeloid cells in their blood. It is apparent that some, if not all, of these patients may have chronic myelopathies. They are considered separately only because none of them have anemia or thrombocytopenia, and the most recent bone marrow examinations continue to be compatible with polycythemia vera. Perhaps some of these patients have what could be described as a "compensated chronic myelopathy." On the average, these individuals have had their disease at least as long and have received as much P^{32} as the patients who developed what we might refer to as "decompensated myelopathies."

On the basis of this analysis of the late complications observed in these patients with polycythemia vera treated with radioactive phosphorus, it is obvious that acute leukemia, chronic leukemia, and other ill-defined chronic myelopathies occur with considerable frequency. The important problem is whether or not the P^{32} therapy played any part in the production of the leukemia or chronic myelopathy. Unfortunately there is no good control series of patients with polycythemia vera observed over a comparable period of time without any form of radiation therapy which is available for comparison with these results. Stroebel, Hall, and Pease[43] compared their series of P^{32}-treated patients with a group of 32 patients who had had polycythemia vera treated by means other than P^{32} and the cause of whose death was known. Four of these patients died of chronic myelocytic leukemia and 4 of them died of malignant tumors, but there were no cases of acute leukemia. However, this was not a real control series as an unspecified number of these patients had received roentgen therapy to the spleen and long bones. Primary polycythemia is a disease in which there is excessive multiplication of all the cellular elements in the bone marrow and in which leukemia at least of the chronic myelocytic variety occurs at times as part of the spontaneous evolution of the disease. Radiation of any sort has certain proved cancerogenic and leukemogenic properties. It is, thus, tempting to speculate that radiation of this already hyperplastic and potentially leukemic tissue by P^{32} might significantly increase the incidence of leukemia. This possibility must remain in the realm of speculation so long as a truly comparable control series of patients untreated with any form of radiation is not available. Even if the

incidence of leukemia were known to be significantly increased by P^{32} therapy, this fact would have to be weighed against the unquestionable advantages of P^{32} therapy of polycythemia vera in terms of even and consistent control of the hematocrit and thrombocyte level with resultant decrease in the tendency for intravascular thromboses to occur. Most of the patients in our series who died of thrombotic complications had been inadequately followed in the months prior to the thrombotic vascular occlusion, and the hematocrit or platelet count (or both) may have been out of control. Careful control of polycythemia vera by P^{32} therapy may increase the average length of life enough to permit a greater incidence of the *naturally* occurring hematologic complications to develop. The authors are of the opinion that P^{32} still constitutes the most valuable form of therapy in the management of primary polycythemia, but the possible hazards should be kept clearly in mind.

CURRENT METHOD OF THERAPY USED BY THE AUTHORS

It is the present practice of the authors to treat all patients with polycythemia vera who are under the age of 40 years, and all mild cases at any age, with phlebotomies alone for as long as the disease can be controlled by an average of one or two 500 c.c. phlebotomies performed not more often than every 3 or 4 months. Whenever the phlebotomy requirements exceed these limits, or whenever the red blood cells become markedly hypochromic, radioactive phosphorus therapy is instituted. The older the patient, or rather the greater the degree of arteriosclerosis, the more urgent is the indication for prompt P^{32} therapy.

When the decision has been made to proceed with radioactive phosphorus therapy, the hematocrit is first restored to not over 55 per cent by phlebotomies. The patient is then given between 4 and 5 mc. of radioactive phosphorus solution in a single intravenous injection. It has not been found practical to calculate the dose on the basis of body weight, but, in general, the dose within the range stated is determined on the basis of both the severity of the disease and body weight. Hematocrit, hemoglobin, white blood cell, differential and platelet counts are then obtained at monthly intervals and additional phlebotomies are performed if the hematocrit rises significantly above 55 per cent. Under no circumstances is further radioactive phosphorus given until 3 months after the initial injection, at which time an additional 1 to 4 mc. of P^{32} are given if the hematocrit is significantly above 45 per cent, or if the platelet count is still significantly elevated. After another interval of 3 months, the patient is again re-evaluated and a third injection of 1 to 2 mc. of P^{32} is given, if indicated, using the same criteria. Somewhat less than 10 per cent of patients will require this third injection.

Once a course of radioactive phosphorus therapy has been completed, no further radioactive phosphorus therapy is given for at least one year, and preferably for 18 months. An occasional patient will remain in remission for 6 to 8 years or even longer before additional therapy of any sort is required. However, in most cases the disease will undergo relapse within 9 months to 2 years. If the interval is less than 18 months, phlebotomies are then performed at appropriate intervals in an attempt to control the disease temporarily. In this manner

the total dosage of P^{32} can be kept to a minimum which would seem to be of importance particularly in those patients who are ultimately treated for a period of 15 to 25 years.

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THE TREATMENT OF INFECTIOUS MONONUCLEOSIS

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ALTHOUGH infectious mononucleosis has been recognized as a clinical entity for at least 67 years, following the clinical description by Pfeiffer in 1889,[1] and even though the hematologic picture was accurately characterized 23 years ago by Downey and McKinley[2] and Tidy and Daniel[3] simultaneously, identifying the lymphocyte as the cell form involved, the causative agent of this disease has not yet been identified. It is axiomatic that specific treatment of a disease is rarely possible without first identifying the causative agent. It is therefore likely that treatment of infectious mononucleosis will remain on a symptomatic basis until the etiologic factor is identified. Although there is rather uniform agreement among workers in this field that the causative agent is a lymphotropic virus, this has by no means been proved. Under the limitations of these circumstances, therefore, the important advances in treatment have been confined to management of the complications and a consideration of this topic necessarily occupies the main portion of this discussion.

GENERAL PRINCIPLES OF TREATMENT

Most cases of infectious mononucleosis are undoubtedly quite mild, and therefore they are often not recognized and are regarded as instances of coryza or influenza. Such mild forms probably constitute the bulk of cases of this disease. It is therefore in the more uncommon instances when the patient is quite ill that a review of the resources available to the physician is needed.

Reported uses of convalescent human serum[4] and gamma globulin[5] and the various newer chemotherapeutic and antibiotic agents have not importantly, if at all, modified the natural course of the disease, except in certain special instances where the antibiotics can be used with profit. The use of corticosteroids may be helpful in some of the complications to be referred to below. There are clearly advantages and disadvantages in employing these substances, and it would seem best not to use them in routine management. In general, therefore, the management of a simple case of infectious mononucleosis should be directed along two lines: (1) symptomatic therapy and (2) recognition of important complications.

The management of the average case resolves itself into employment of the simplest of symptomatic measures. Commonly, confinement to a bed-chair routine as long as the fever persists and the employment of aspirin for greater comfort is all that is necessary. Occasionally a membranous type of pharyngitis

and/or tonsillitis dominates the clinical picture. When this occurs, it is best to obtain a throat swab for smear and culture for purposes of identifying secondary invaders, especially Vincent's organisms or hemolytic streptococci. If either of these groups of organisms is present, treatment with penicillin is advisable. Supplementary to these measures, warm alkaline solutions for lavage of the throat and perhaps the application of an ice collar may bring added relief.

COMPLICATIONS REQUIRING SPECIAL TREATMENT

In recent years there has been a steady increase in reported deaths, most of these from a ruptured spleen. However, deaths have also been reported from respiratory paralysis (Guillain-Barré syndrome) as well as a scattering of other terminal events which occur quite rarely, including pulmonary edema, laryngeal spasm, septicemia (or toxemia), nasopharyngeal hemorrhage, and laryngeal edema, to name the most important. It would therefore seem that careful attention to the onset of these possible complicating features that occasionally cause death becomes the major concern of the physician.

Hepatitis.—The vast majority of cases, perhaps even all of them, present some degree of liver involvement. This may be so minor that a battery of liver function tests is required to recognize the participation of the liver in the disease picture. On the other hand, such severe involvement may occur that the patient is deeply jaundiced, nauseated, and often vomits. Punch biopsy specimens show this to be indistinguishable from the usual histopathology of an infectious hepatitis. It is probable that the infectious agent of the primary disease rather uniformly, but in varying degrees, attacks the parenchymal cells of the liver.[6] The condition has been fatal[7] and progression to cirrhosis has been reported.[8] While presently available data do not make it possible to state the entire long-range implications of such severe hepatic involvement, it appears proper to state that, from general experience with epidemic infectious hepatitis, the usual care with bed rest and attention to good caloric intake is at least useful in the more pronounced forms of the hepatitis of infectious mononucleosis.

Rupture of the Spleen.—The occasional occurrence of spontaneous rupture of the spleen represents the most common cause of death in infectious mononucleosis. This incident may be confused with the abdominal pain sometimes present from involved intra-abdominal lymph nodes but is usually readily identified because of the rapidly progressing shock, localization of pain in the splenic area, often with reference to the left shoulder, and the physical signs of blood within the abdominal cavity. The rupture sometimes follows strain by the patient, as in the act of defecation and possibly also may be caused by vigorous palpation of the spleen on physical examination. Apparently the basic structure of the spleen is weakened by the disease, the most important factor being a dissolution of the capsule which gives way under the influence of the enlarging organ. Therefore trauma, as well as rapidity of enlargement of the spleen, is an important factor. Recognition of this event is of life-saving importance as immediate splenectomy is mandatory.

Thrombocytopenic Purpura and Hemolytic Anemia.—Not rarely, patients with this disease may show signs of a hemorrhagic diathesis or of a hemolytic

anemia (hypersplenism) which can be proved to be due to low blood platelets (hemorrhage) or intravascular hemolysis (anemia) by the appropriate laboratory observations. Hemorrhagic tendencies because of reduced blood platelets may result in a fatal termination through bleeding unless the condition is properly recognized and treated. It is rarely necessary to remove the spleen in the treatment of thrombocytopenic purpura secondary to infectious mononucleosis, although this has been done in our clinic as well as elsewhere[9] in certain instances where bleeding was profound and apparently unremitting. In the vast majority of cases, treatment by any of the corticosteroids, together with supporting whole fresh blood transfusions, will overcome the hemorrhagic manifestations. For patients under the age of 10 years, the prescription of Prednisone or Prednisolone in dosages of 10 mg. every 6 hours, and for the remaining ages, up to 25 mg. every 6 hours may be required. This treatment, continued for some 5 or 7 days, will be attended with a rise of platelet levels well above bleeding range, following which the steroid can be rapidly tapered off and then eliminated. When there is complicating hemolytic anemia, usually transfusions alone or transfusions supplemented by steroids in a dosage identical with that used for treating the secondary thrombocytopenic purpura will easily overcome this complicating event.

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Involvement of the Nervous System.—Involvement of the central nervous system by infectious mononucleosis may be present in the form of meningitis, encephalitis, meningoencephalitis, acute polyneuritis, or as a peripheral neuropathy. These complications have been critically discussed by Bernstein and Wolff.[10] Involvement of the nervous system seems to occur in less than 1 per cent of cases; nevertheless, because of the possible occurrence of respiratory failure, the physician must be acutely aware of possible dangers in this type of complication. The most common time for this manifestation seems to be between the first and third weeks of the onset of the illness and, in many cases, the usual clinical picture of infectious mononucleosis is almost completely absent. Respiratory failure may be due to central or peripheral involvement. The lesions consist of degenerative changes in the cells of the respiratory center in the medulla and hemorrhages and degenerative changes of the ganglion cells of the cerebrum, pons, medulla, and, occasionally, the posterior horns at several levels of the spinal cord. It must be said, however, that in all of these cases, there is rather diffuse involvement of ganglion cells and nerve tracts with varying stigmas of inflammation. These often bear the general label of "Guillain-Barré syndrome." It appears that, in this complication, the employment of corticosteroid therapy in full doses is important, although it is by no means certain that the exhibition of this substance exerts any effect beyond that of symptomatic relief of the inflammatory swelling that accompanies the lesions. The use of steroids appears to be without great danger and, because of the occasional death that occurs in this manifestation, may exert an effect other than that of mere symptomatic improvement. At times, the artificial respirator may need to be employed, and it is therefore important that all patients with central nervous system involvement be transferred to a hospital where this type of apparatus is available upon a moment's notice.

Cardiac Involvement.—Electrocardiographic abnormalities are sometimes seen in infectious mononucleosis. They were first reported by Longcope in 1922,[11] who noted premature ventricular contractions, inverted T waves in the electrocardiogram, systolic mitral murmur, and, in one case, an enlarged heart. Other electrocardiographic changes subsequently reported consisted of abnormal T waves, prolonged PR intervals up to 0.40 second, deviations of the S-T segments, low voltage, and minor slurring of the QRS complexes. There have been few post-mortem examinations; however, in those reported, interstitial infiltrations of abnormal lymphocytes in the myocardium have been found and suggest that many of the electrocardiographic changes described are due to varying degrees of myocarditis. For the therapist, this would mean that if any abnormality of the heart is noted at the time of physical examination of a patient with infectious mononucleosis an electrocardiogram should be taken. If clinical or electrocardiographic evidence of myocarditis is noted, activity should be restricted, or even bed rest prescribed.

CONCLUSION

It will be seen from the above brief summary of the treatment of infectious mononucleosis that the important part of the therapeutic management of this disease lies in the earliest possible recognition of the complications of this disorder. Careful attention to detail and treatment and sometimes bold treatment, is necessary if the course of the complication progresses. Fortunately, most of these complicating features abate spontaneously and require only conservative management. While serious developments in this disease are uncommon, the over-all incidence of perhaps 5 per cent of the various complications listed above makes it imperative that cases of this disease be kept carefully under observation until all likelihood of serious events has disappeared. It should be emphasized that the remaining 95 per cent of these cases should receive no therapy other than a variable amount of enforced bed rest and the employment of analgesics and local measures.

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LEUKOPENIA: ITS MECHANISM AND THERAPY

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LEUKOPENIA occurs in association with many clinical disorders and may be of any degree. It may require no special therapy or it may demand very active and vigorous therapy, depending upon its degree, its underlying cause, and upon the presence or absence of secondary infection. It should be looked upon as one manifestation of some clinical disease, much as are fever, anemia, purpura, and other symptoms and signs. In the vast majority of instances leukopenia is low-grade, produces no symptoms, and disappears with relief of the underlying clinical disorder. This is particularly true in some of the acute infectious diseases (such as typhoid fever, brucellosis, and viral infections), in anemia due to deficiency of B_{12}, and/or dependent upon folic acid deficiency. In general, it may be considered that leukopenia will not produce symptoms or cause difficulty, if the peripheral white blood cell count does not go below 3,000 per cubic millimeter and if the neutrophils are not depressed below 20 per cent. This does not mean that leukopenia in this range should be ignored. However, it does indicate that in such instances leukopenia is to be looked upon as one indication of some abnormal disorder which should be uncovered, if possible. Thus, low-grade leukopenia in a person taking some drug capable of depressing bone marrow function would indicate discontinuation of the drug or, at the least, very close observation as to the trend of the white blood cell level. Likewise, it might be one of the first indications of aplastic anemia, refractory anemia, or other serious disease affecting the bone marrow. Unfortunately, in some such instances the disease process has advanced to a stage where little can be done to relieve the disorder. This is particularly true as regards chronic low-grade radiation exposure since leukopenia due to this may not be detected until after irreversible changes have occurred. The best way to prevent overexposure in such circumstances is the proper use of dosimeters. The time-honored use of repeated white blood cell and differential counts for detection of irradiation exposure frequently fails as an early indication of overexposure due to the fact that the normal range of such counts is wide. Thus, a white blood cell count of 5,000 to 10,000 and percentages of 20 to 40 of lymphocytes and 45 to 75 of neutrophils are generally considered normal, whereas in a particular individual 5,000 for a total count and 20 for the per cent of lymphocytes or 45 for the per cent of neutrophils might be distinctly low values. Unless an individual has had many and *very frequent* blood studies it is impossible to detect early changes due to irradiation. Commonly blood studies on individuals engaged in activities which might be associated with overexposure to irradiation are made at intervals of 4 or more

TABLE I. CLINICAL CLASSIFI

I	II	III	IV
LEUKOPENIA DUE TO INFECTIOUS DISEASES	IDIOPATHIC LEUKOPENIA	TOXIC LEUKOPENIA	LEUKOPENIA ASSOCIATED WITH INTRINSIC MEDULLARY DISEASE
1. Bacterial—e.g., typhoid fever, brucellosis, some overwhelming infections	1. Acute—(rarely)	1. Acute leukopenia due to	1. True aplastic anemia
2. Viral—e.g., influenza, epidemic hepatitis, "atypical" pneumonia, measles, and roseola infantum	2. Chronic	A. Drugs (1) Immune—e.g., amidopyrine (possible) (2) Cytotoxic—e.g., Myleran, nitrogen mustards, etc. (3) Metabolic antagonists—e.g. A-methopterin (4) Mechanism unknown—e.g., sulfonamides	2. Pseudoaplastic anemia
3. Protozoal—e.g., malaria and kala-azar	3. Recurrent and/or cyclic	B. Radioactivity	3. Myelophthisic anemia
4. Platyhelminthic—e.g., chronic schistosomiasis		2. Chronic leukopenia due to	(a) Carcinoma with metastases to the bone marrow (rarely)
		A. Drugs	(b) Leukemia, leukopenic type or phase
		B. Radioactivity	(c) Hodgkin's disease (rarely)
			(d) Lymphosarcoma (rarely)
			(e) Myelosclerosis (occasionally)
			(f) Multiple myeloma

weeks and are of no practical value in preventing overexposure. When leukopenia is obvious by these methods, much more irradiation exposure has occurred than should be allowed.

Leukopenia may be due to any one of a variety of mechanisms. As pointed out previously,[37] it may be the result of one or the other of the following mechanisms:

1. Diminished manufacture of white blood cells as a direct consequence of (a) simple inhibition—that is, general slowing down of or obstruction to the manufacture of white blood cells, (b) "maturation arrest," or the cessation of or marked slowing of the manufacture of white blood cells *at one particular stage of maturation*, (c) aplasia of the bone marrow, and (d) infiltration of the bone marrow with foreign cells.

CATION OF LEUKOPENIA

V	VI	VII	VIII
LEUKOPENIA ASSOCIATED WITH SPLENIC DYSPLASIA, SPLENOMEGALY, AND/OR HEPATOMEGALY	NUTRITIONAL LEUKOPENIA	HOARDING LEUKOPENIA	IMMUNOLOGIC LEUKOPENIA
1. Cirrhosis of the liver	1. Deficiency of B_{12}	1. Anaphylaxis—foreign protein reactions	1. Due to antileukocytic antibodies (rare)
2. Chronic congestive splenomegaly	(a) Due to deficiency of intrinsic factor	2. Due to transfusion of blood (very rarely)	2. Due to drugs—e.g., amidopyrine
3. Splenic idiopathic leukopenia	(b) Secondary to abnormal intestinal physiology		3. Paroxysmal nocturnal hemoglobinuria (?)
4. Gaucher's disease	(c) Due to gastrectomy		4. Lupus erythematosus disseminatus (?)
5. Massive derangement of the spleen as with tuberculosis or syphilis (at times)	(d) Due to deficiency of B_{12} in diet		
6. Felty's syndrome	2. Deficiency of folic acid		
7. Certain hemolytic anemias (at times)	(a) Macrocytic anemia due to diet or poor absorption		
8. Agnogenic myeloid metaplasia of the spleen (at times)	(b) Sprue and/or idiopathic steatorrhea		
	(c) Macrocytic anemia of pregnancy		
	(d) Antifolic acid drugs		
	(e) Secondary to action by drugs on bacteria in the intestine		
	3. Other poorly understood dietary deficiencies		
	4. Malnutrition		
	5. Hypochromic anemia, chronic, of long standing		

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2. Increased elimination of white blood cells such as *may* occur when very large numbers of cells are lost in infected areas and when cells are eliminated in very large numbers through usual channels, e.g., in the gastrointestinal tract, the lungs, and the spleen or liver.

3. Increased rate of destruction of the white blood cells in the peripheral blood due either to abnormal white blood cells or to abnormal substances in the blood channels which cause destruction of the white blood cells.

4. Redistribution of the white blood cells in the vascular channels such as occurs when foreign proteins are injected.

5. Redistribution of the white blood cells in the body as a whole, as is seen at times in the leukopenic phases of leukemia.

It should be emphasized that the leukocytes in the blood represent only a small fraction of those in the body. The count at any one period should not be considered as revealing whether the rate of utilization is high, low, or normal. However, persistently low counts, in most instances, can be taken as reflecting a depleted marrow reserve, usually the result of production being less than the destruction, in the same way that a persistently elevated neutrophil count can be taken as a reflection of adequate marrow reserve where production is equal to destruction of white blood cells. Much information relating to the dynamics of leukopoiesis has been accumulated in this laboratory during the past few years by the use of leukopheresis. Results of this work have been reported elsewhere.[15,16,38] It is our feeling that the bone marrow represents the main, if not the only, reserve supply of granulocytes available for release into the circulation under *most* but *not all* conditions. This should not be taken as excluding redistribution of leukocytes in the vascular channels and body tissues in general, and the other mechanisms mentioned as possible causes of leukopenia. In other words, diminished levels of white blood cells eventuating in depleted marrow reserves may be the result of any of the mechanisms mentioned above. The white blood cell reserve is of tremendous importance and, in the last analysis, *may* be the principal determining factor as to whether leukopenia, leukocytosis, or a normal white blood cell level exist. Much additional work is indicated on this problem. One set of observations has interested us a good deal recently. This relates to the leukopenia with subsequent leukocytosis occurring after injections of typhoid vaccine. We had felt that the white cells in this reaction disappeared as a result of sticking to the vascular walls in various areas of the body and that they were subsequently released causing leukocytosis. It would seem from our results[16] that the leukocytosis is not due to release of the cells stuck to the vascular walls but to white cells released from the bone marrow. In other words, it looks as though the cells taken from the blood channels and plastered to the vascular walls are destroyed and do not recirculate.

These considerations of the physiology and dynamics of the white blood cells are important from the point of view of a clear understanding of the leukocytes, but they have not advanced to the point where they can be applied to all of the clinical conditions associated with leukopenia. However, it is of importance that these mechanisms be appreciated and understood when considering the obvious clinical manifestations of leukopenia.

A clinical classification of leukopenia has been reported previously.[39] It is here presented with modifications to allow for some developments during the interval since its publication (Table I).

When one attempts to explain this classification in terms of the various physiologic mechanisms responsible for leukopenia, much difficulty is encountered. Thus, as pointed out previously,[39] little is known as to the exact process responsible for the leukopenia accompanying acute infectious diseases. Obviously, it could be due to (1) increased destruction and/or elimination of white blood cells, (2) diminished manufacture of white blood cells, or (3) a combination of (1) and (2). No detailed studies of leukopenia in bacterial infections have been made. Boyd[3] has suggested that changes in the bone marrow are responsible for the leukopenia in typhoid fever but there are no definitive observations in this connection.

It would seem that there is a good reserve of cells in the marrow since it is well known that leukopenia may change to leukocytosis with the advent of complications, such as perforation. Goudsmit and van Loghem[29] have reported the isolation of "several bacterial strains from an infected serum which had marked 'agglutinative' properties." They were able to demonstrate the acquisition of leukocyte agglutination power by normal serum following infection with these bacteria. This lends support to the possibility of increased destruction of the white blood cells as one explanation for leukopenia in some infections. Extensive studies were made several years ago[36] on the leukopenia occurring in infectious feline agranulocytosis, which is a disease of spontaneous origin in the cat and is due to a filterable virus. The leukopenia in this disease is associated with marked reduction of the myeloid elements of the bone marrow and absence of differentiation of the myeloid cells. It would seem, therefore, that bone marrow changes are responsible for at least some of the leukopenia in animals with this disorder. However, this does not mean that the same mechanism is present in other viral infections. Certainly we know that in most viral infections such striking changes in the marrow do not exist. Lucke[44] has reported moderately hyperplastic marrow in infectious hepatitis. There is no pertinent information, to my knowledge, on this point in regard to protozoal infections.

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Relatively few instances of acute idiopathic leukopenia have been encountered since Madison and Squier's reports,[45,61] in 1934, showing that amidopyrine was responsible for many of the cases of acute leukopenia occurring at that time. Chronic idiopathic leukopenia is seen on occasion and presents a major problem. Various types and forms exist and tax the ingenuity of those into whose hands they fall. In some instances, leukopenia is the only manifestation of any abnormality in the individual and may exist without any other hematopoietic abnormality. In other instances, abnormalities in one or the other formed elements of the blood may appear with or without splenomegaly.

The recurrent or cyclical type of idiopathic agranulocytosis is a rare and interesting clinical disorder. The first report was by Leale[40] in 1910. In 1935, Stephens and Lawrence[63] reported this disorder in a white woman 38 years of age and reviewed the literature up to that time. Agranulocytosis in their patient coincided with the menstrual cycles as had been true of the patient reported by Thompson.[66] No relief resulted from bilateral salpingo-oophorectomy. Reimann and de Berardinis[56] collected 16 cases from the literature in 1949, and suggested that this entity be included in their group of periodic diseases. More recently, Coventry[14] has reported another case. Splenectomy was done and failed to affect the periodicity of the neutropenic cycle, although there was some persistent rise in the total white blood cell count. He reviewed the reported effects of splenectomy and came to the conclusion that it was beneficial if the spleen was considerably enlarged but that it was of no value in young patients with normal or slightly enlarged spleens. These conclusions are based upon the results obtained in 9 patients and must, therefore, be taken with reservations. One can raise the question as to whether those patients who showed improvement should not have been considered as having primary splenic neutropenia rather than idiopathic cyclical neutropenia. The presence of splenomegaly should always

raise the question of the leukopenia being secondary to splenic dysplasia. No satisfactory explanation for this unusual clinical entity is known to the author.

The term toxic leukopenia has absorbed most of the disorders formerly classified as acute idiopathic leukopenia. Since the clear-cut demonstration by Madison and Squier, in 1934,[45] of the ability of amidopyrine to produce agranulocytosis in certain individuals, many drugs have been shown to have this same capacity to cause leukopenia and/or agranulocytosis. Most of the patients with acute agranulocytosis seen by me in the past 15 to 20 years have been shown to have leukopenia secondary to toxic drugs or irradiation. It should be recognized that drugs and chemical agents do not all produce leukopenia by the same mechanism. Thus, amidopyrine is generally considered to produce its effect as a result of a true immunologic reaction, whereas sulfanilamide is thought to act in some other way. The exact mode of action of the many drugs known to be capable of producing leukopenia is not known and demands further study. Hypersensitivity can be offered as the explanation for the action of some, but not all. Other drugs, such as Amethopterin, produce their effect by acting as metabolic antagonists. Still others are said to be cytotoxic. Whether all of the so-called cytotoxic agents have the same basic mechanism cannot be said, but they do have enough in common to be given a separate category. Agents in this group include nitrogen mustard, colcemid, Myleran, and irradiation. Another group consists of those drugs that change the flora of intestinal bacteria or act upon the bacteria in the intestine in such a way as to interfere with the development of some substance or substances necessary for the manufacture of white blood cells. This has been amply demonstrated in the rat.[2,60,34] Finally, there is the largest group of all, characterized by a totally unknown mechanism.

Most of the drugs that produce acute leukopenia do not cause the chronic variety, since with elimination of the drug the individual recovers or, in more severe cases, succumbs. Some agents, however, such as benzene, gold compounds, irradiation, and arsenicals are capable of producing leukopenia which may not disappear with discontinuation of the drug or agent. The mode of action in these instances is not thoroughly understood. Morphologic aplasia may be present in some cases but, in many, this is absent and we are left only with the unsatisfactory term functional aplasia.

Irradiation leukopenia has been studied very intensively in recent years. It has been established that this is the result of mitotic injury to the precursor cells but just how this injury is produced is not known. Because of the likelihood of greater exposure to irradiation in the future a detailed discussion of this type of leukopenia will be given.

The demonstration by Jacobson and his associates,[32] in 1949, of the reduction of mortality in mice given LD 50 whole body irradiation by shielding of the spleen stimulated tremendously investigative activity dealing with the modification of irradiation injury. Their work was further extended so as to show a diminution in mortality from irradiation injury in mice, even if the shielded organ was removed within as short a space of time as 15 minutes, although a maximum effect did not occur unless the shielded spleen was left within the animal for as long as one hour. It was also shown by this same group of investigators that mortality was diminished by the intraperitoneal implantation of splenic tissue as late as 2 days

after exposure to irradiation. Soon after this report, Lorenz and associates[42] demonstrated that protection against irradiation injury in the mouse could be obtained by the intravenous injection of homologous bone marrow. Rekers[57] is credited with having first conceived this idea but his results were only equivocal in the irradiated dog.

Much additional work has been done along these lines since these two original and important reports. Some of the more significant findings are: (1) Rather marked variation in response, in different species or strains. Thus, while hastened hematologic recovery and increased survival of rats and guinea pigs result from splenic shielding, only a minimal protective effect is produced in the rabbit.[33] (2) Retention of the ability by rabbits to produce antibodies after whole body exposure to 800 r if the spleen or the appendix is shielded.[33] (3) Reversal of the otherwise lethal effect of irradiation by the injection of spleen or bone marrow even as late as 2 or 3 days after an animal has been exposed to a lethal amount of radiation.[33] (4) Protection of irradiated mice by injection of the bone marrow of the rat.[12,43] (5) The ability to survive larger amounts of irradiation to the whole body if given in 2 doses with an interval between them. This occurs regardless of whether the abdomen is irradiated first or last.[64] (6) Demonstration of the fact that the DNA content of the spleen is a sensitive biochemical index of recovery following x-radiation exposure.[11] (7) Inability of the cytoplasmic and supernatant fractions of mouse spleen cells[6,10] to protect against irradiation. Brown and associates showed that this activity was, likewise, absent in cytoplasmic and supernatant fractions of mouse bone marrow. The evidence as regards the nuclear fraction was inconclusive.[8] (8) Beneficial effect of thigh shielding and marrow cell injection in the absence of the spleen.[6] (9) Promotion of recovery, as evidenced by regeneration of hematopoietic tissue and by survival, as a result of intravenous injection of leukemoid blood of tumor-bearing mice.[13] These investigators cite references tending to exclude the red blood cells, the lymphocytes, and the platelets. In their opinion, the granulocytes were responsible for the protection against radiation injury. They found that injections of this leukemoid blood afforded protection when given as late as 2 days post-irradiation but not at later intervals. (10) Different effect on irradiation injury of isologous bone marrow as compared with that of homologous bone marrow.[31] Hirsch and associates present data which show that the factor in bone marrow responsible for thymic weight regeneration (their assay criterion for effect on irradiation injury) is highly strain specific. Isologous marrow is shown to be consistently effective, whereas homologous and heterologous marrow give no evidence of activity. They present considerable evidence against the acceptance of recent work with various species or strain-specific markers, such as the histochemical phosphatase reaction, morphologically identifiable chromosome translocations, and red blood cell immune responses,[41] as proof that survival of irradiated animals after homologous or heterologous marrow injection is due to the same mechanism as that which operates in the case of isologous marrow. They advance the hypothesis that the heterologous effect is fundamentally different from the isologous effect.

This short synopsis is sufficient to show that irradiation effect in the rat, guinea pig, mouse, and rabbit can be modified considerably by the injection of

bone marrow or splenic cells intravenously or intraperitoneally. The effect on the white blood cell picture is only one of the favorable results obtained. It is not possible to say whether the beneficial results are due to the living cell, to an exogenous humoral factor, or to an inflammatory factor with resulting stimulation of granulopoiesis as suggested in the work of Cronkite and Brecher.[18] It is hoped that this short interval of 48 hours during which certain procedures will produce modification of radiation injury will be extended indefinitely with further study and experimentation in this important field. One is tempted to predict that the treatment of irradiation injury will progress to the point where damage from irradiation can be controlled and that this may lead to a better understanding and treatment of the other types of leukopenia. It should be noted that beneficial effects on leukopenia from bone marrow preparations have been reported in the past but have not been substantiated.[7,46,47,68] All of these investigators used bone marrow extract rather than bone marrow cells.

Leukopenia associated with intrinsic medullary disease requires no detailed comments. Leukopenia in association with morphologic aplasia of the bone marrow is, obviously, due to failure to manufacture white blood cells; but the answer is not so obvious with the other situations given under this heading except myelosclerosis, which, of course, is associated with a diminished total amount of bone marrow. Maturation arrest is often given as the explanation for some of the disorders listed under this category, but this is a vague concept which cannot be very clearly substantiated. We can state what we mean by it but we cannot, in the present state of our knowledge, prove that it actually exists. No one has ever shown that maturation stops in these cases nor has anyone excluded very rapid and sudden destruction of all cells beyond a certain stage of development.

Multiple factors may be present in some of these disorders. In leukemia, Hodgkin's disease, and lymphosarcoma there is, in certain instances, splenomegaly associated with deranged splenic activity. When this is the case, the same mechanism may be at fault as in the conditions listed in Group V in which splenomegaly is a common factor. The mere fact that splenomegaly and/or splenic dysplasia is present in all the members of this group does not prove, however, that the same mechanism as regards leukopenia is present in all of them. However, one can consider an abnormal spleen as one possible cause for the leukopenia in these conditions. It is not clearly understood how leukopenia is produced in the disorders associated with splenic dysplasia, splenomegaly, and/or hepatomegaly. Doan and Wright[24] have advanced the idea that it is due to increased destruction of the white blood cells by the reticuloendothelial cells of the spleen but, while there is some morphologic evidence of this, there is no proof that this is the real explanation for the leukopenia. Indeed, the finding of morphologic changes in the bone marrow, interpreted by some as maturation arrest, raises the question of inhibition or deranged manufacture.

Nutritional leukopenia seems most probably due to diminished or disturbed manufacture of the white blood cells secondary to the deficiency of some agent necessary for their manufacture. The restoration of normal myeloid activity with administration of the substance in which the individual is deficient is a strong indication that this is the correct explanation. Further, the demonstration of large cells (i.e., macropolycytes in the marrow and the peripheral blood) indicates

a disturbance in maturation or manufacture. This finding has been shown to be common to cells in certain other organs in pernicious anemia and has been taken to indicate a general effect of vitamin B_{12} on cell growth.[30] Folic acid may act in a similar or closely related way. Less is known as to what is responsible for the leukopenia one sees at times in malnutrition and in long-standing iron deficiency anemia.

Hoarding leukopenia refers to leukopenia which occurs following the injection of hydrophile colloids such as gelatin, globulin, and fibrinogen. This is generally referred to as a reaction to foreign protein, of which typhoid vaccine is a good illustration. It is thought to be due to the sticking of the white blood cells, particularly the neutrophils, to the walls of the venules or paracapillaries in some of the internal organs, e.g., brain, lungs, spleen, and omentum. That such a mechanism actually does play a part in leukopenia of this type can be and has been demonstrated by direct observation of the blood vessels in the omentum following the injection of typhoid vaccine or similar substances.[35] It cannot be said that this is the only mechanism at fault but it would seem adequate.

Leukopenia occurs very rarely following the transfusion of blood and in the absence of any demonstrable red blood cell type incompatibility. In some instances, this is, presumably, due to a foreign protein type of reaction and, thus, should be considered as hoarding leukopenia. In other instances, it may be due to (1) the presence in the donor's blood of leukoagglutinins for the white blood cells of the recipient; (2) a nonspecific response of the white blood cells to a true immunologic reaction as reported by Waksman[67]; (3) false positive leukoagglutination in association with the administration of unrecognized contaminated blood as commented upon by Goudsmit and van Loghem[29]; and (4) other less well-known mechanisms.

The last group of leukopenias has been designated immunoleukopenia. Leukopenia is thought to be due in this group of disorders to antileukocytic antibodies in the involved subject's blood. In most instances, there is no clear explanation for the presence of these antileukocytic antibodies. Certain drugs are thought to be capable of causing the development of autoleukoagglutinins. In particular, amidopyrine is considered by some as producing hypersensitivity in susceptible individuals in this way. In these instances, it has been suggested[51] that the drug reacts with a protein in the patient to form a compound which acts as an antigen. This results in the formation of antibodies, which, in this situation, are considered as becoming attached to the white blood cells. Hence, reaction between antigen and antibody results in agglutination of the white blood cells.

The situation as regards other antileukocytic antibodies is far from clear. It has been shown that there is more than one substance in white blood cells capable of acting as an antigen.[59] It is also possible that different types of white cells may be capable of acting as different antigens. Chew, Stephens, and Lawrence[8] demonstrated, in 1936, as had been done previously, that antineutrophilic serum could be produced by the injection of neutrophils of one species repeatedly into another species. Much activity has developed in this field in recent years. No attempt will be made to cover the recent literature since this has been done in the reports by Finch and others[26,27] and Moeschlin and his

associates.[50] White blood cell antiserum is species specific but no one has ever demonstrated that different antisera can be produced in this way for different members of the species. Antilymphocytic serum also has been demonstrated in a few instances.[9,19,48] Attempts to produce specific antisera for other types of white blood cells have not been successful in the hands of most investigators, although Steinberg and Martin[62] presented data which they felt strongly suggested the presence of a specific cell-antigen or antigens to mature lymphocytes, mature granulocytes, immature lymphocytes, and immature granulocytes.

Leukoagglutinins have been demonstrated in human serum in repeated instances.[4,20-23,28,49,51,62] Dausset[20] reported that he had not found such leukoagglutinins in 1,000 normal sera. However, he found leukoagglutinins in 60 of 700 pathologic sera, 85 per cent of these being from leukopenic individuals and 90 per cent being from patients who had had multiple transfusions. The explanation for the presence of these leukoagglutinins is unknown. If there are different types of leukocytes in the same way as there are different types of red blood cells, leukoagglutinins of the isotype could develop in individuals receiving multiple transfusions but these leukoagglutinins should not agglutinate the recipient's white blood cells. Further, one could ask why such leukoagglutinins would not develop in nonleukopenic subjects or why they should be found mainly in leukopenic subjects. Observations as to the presence of such leukoagglutinins in leukopenic subjects *prior* to transfusion would be helpful in understanding this.

Much more work is needed in this area before a clear picture can be obtained. As mentioned above, there is more than one substance in white blood cells capable of acting as an antigen. Hypothetically, one can imagine a situation in which one or more of these substances is changed as a result of some abnormal situation. In such a circumstance, it is conceivable that this substance would act as a foreign antigenic agent with the resulting formation of antibodies. It can be conceived, also, that abnormal antigenic substances may occur in the plasma under certain conditions, in which case one or more of these substances could cause the production of antibodies, which could attach themselves to the white blood cells, thus causing their agglutination and subsequent destruction. Some analogy to these hypothetical situations is found in the red blood cells in certain unusual circumstances.[52] There is no proof that such mechanisms do exist, nor should it be considered that these are the only ways in which leukoagglutinins could develop in the blood.

With this background as to the mechanisms that may be involved in leukopenia, one can approach the individual therapeutic substances or procedures that are indicated for the control of this disorder. Obviously, the most important procedure is eradication of the underlying disease whenever this is possible. Thus, cure or correction of pernicious anemia, sprue, typhoid fever, brucellosis, and so forth, results in disappearance of the associated leukopenia. Elimination of the responsible drug will in many instances result in cure of the leukopenia but this is unfortunately not true in all instances. The number of such refractory cases is reduced by close observation of those receiving myelotoxic drugs and discontinuation of such drugs when leukopenia starts. If drugs are continued in the presence of severe leukopenia, irreversible changes may and do occur. It must be remembered, also, that some of these drugs are prone to produce chronic

changes. In most instances, close watch over the white blood cell level during administration of the drugs or agents and discontinuation with the advent of any leukopenia will circumvent chronic changes. However, in some clinical disorders one is forced, in order to get the desired effect of the drug or agent, to proceed after mild leukopenia develops, only stopping with the advent of leukopenia of appreciable degree. This is particularly true with irradiation therapy for malignancy.

The use of antibiotics aids tremendously in preventing infection, which is the major complication of agranulocytosis. These agents are, of course, very valuable in combating infection once it has occurred. Obviously, it is of advantage to prevent infection, if possible. Thus, in all acute agranulocytoses antibiotic administration is indicated. Penicillin should be given in doses of 600,000 to 1,200,000 units intramuscularly daily throughout the period of agranulocytosis. This drug is advised routinely since it is the most effective agent against the most common bacterial invaders, the gram-positive cocci. It should be recognized that penicillin-resistant organisms, such as penicillin-resistant staphylococci and gram-negative bacilli, may enter the picture at any time. For this reason, some advocate the routine administration of wide-spectrum antibiotics. It seems to me preferable to omit these agents unless the clinical picture of infection occurs during the course of penicillin therapy. In such an event, tetracycline or one of the related wide-spectrum antibiotics should be given in doses of 0.5 Gm. every 6 hours, after the proper bacteriologic procedures have been performed for the demonstration of the organism or oganisms that are responsible for the infection.

In those situations where these drugs are poorly tolerated or do not produce clinical improvement (particularly if resistant staphylococcal infections are suspected), other antibiotics such as erythromycin or chloramphenicol should be given while diagnostic procedures are underway. If gram-negative bacillary infections are present, chloramphenicol or one of the less commonly employed antibiotic agents, such as polymyxin, would be the agent of choice. In other words, the antibiotic therapy is that which would be indicated in infections whether or not leukopenia were present. It is obvious that blood cultures and other individual bacteriologic studies should always be made when the patient with agranulocytosis comes under observation and before antibiotics are begun.

The administration of cortisone, hydrocortisone, prednisone, or related steroids should be given some consideration. In most instances, these substances should be withheld. However, in the presence of extreme toxicity they *may* be of benefit. One other possible indication is in immunoleukopenia. It is possible that they may be of some help in this situation due to their effect on the immune reactions. This is only theoretical and lacks clinical proof.

If arsenic, gold salts, mercury, or other heavy metals are responsible for the leukopenia, BAL (British anti-lewisite) (2, 3-dimercaptopropanol) may be tried. The following is the recommended mode of administration of this substance: 3 mg. per kilogram (10 per cent in oil), intramuscularly every 4 hours for the first and second day; four injections on the third day; and twice daily thereafter for 10 days or until complete recovery. This author has had occasion to use this therapy on only a few occasions, in none of which it seemed to produce any benefit.

Pentnucleotide has been of no value in the cases which I have seen treated with this substance. The same may be said of transfusions of blood *unless* anemia is present.

Various general or specific measures should be used as indicated. Thus, mouth lesions require mouth washes, local applications, and so forth. Fever and dehydration should be handled as in any other situation.

The foregoing statements have been directed largely at acute leukopenia. In the chronic form of the disorder antibiotics are not generally used except when actual infection develops. It is remarkable how free from infection some of these cases may remain for long periods of time, whereas others may have frequent recurrent episodes of infections. In these latter cases, prophylactic penicillin or broad-spectrum antibiotic therapy may be used.

Splenectomy must be considered in the chronic disorder, particularly when splenomegaly is present. In those instances in which the leukopenia is due to abnormal destruction of white blood cells or inhibition of their production by the spleen, removal of the spleen may be of marked benefit. Unfortunately, it cannot be determined whether the spleen is at fault prior to splenectomy. Whenever there is a reasonable question as to the spleen being responsible for severe chronic leukopenia, splenectomy should be done after other measures have failed, provided the general condition of the patient permits. This applies whether or not splenomegaly exists.

The various measures that have been shown to lessen or modify the effect of irradiation, such as (1) cysteine or glutathione when used preirradiation[17,54,55]; (2) maintenance of low temperatures during and after irradiation[1,53]; (3) anoxic conditions during irradiation[25]; (4) splenic shielding during irradiation or transplantation of splenic tissue into the peritoneal cavity of a previously irradiated animal[32]; (5) intravenous or intraperitoneal injections of bone marrow suspensions after irradiation[42]; (6) massive postirradiation cross or replacement transfusions[58,65] and parabiosis[5]; and (7) transfusion with leukemoid blood[13] have not advanced to the point that they are of practical clinical value in either irradiation leukopenia or other types of leukopenia. It is hoped that from these something will evolve which will be of definitive value to acute leukopenia.

SUMMARY

The most important and essential considerations dealing with the treatment of leukopenia are: (1) a good understanding of the mechanism responsible for the condition; (2) eradication or elimination of the causative factor or disease, if such is possible; (3) judicious use of antibiotics; (4) palliative measures as indicated.

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THERAPY OF THE PURPURAS

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PURPURA is a term which may be applied to any instance of intradermal or subdermal extravasation of blood. It is a cardinal feature of numerous disorders. Some types are of special interest to the hematologist; this group includes defects of capillary hemostatic mechanisms, all derangements of platelet number or function, and coagulation abnormalities. Boundaries of definition are not precise, however, and every cause for formation of petechiae and ecchymoses must be considered in differential diagnosis (Table I).

Since purpuras of even primary hematologic interest embrace a multitude of causes, and since space is limited, consideration of all varieties will not be possible. Even with omission of nonhematologic syndromes, additional restrictions must be set on topics to be considered. In the following discussion of therapy, diseases requiring self-evident measures will not be reviewed, e.g., scurvy or bacteremia. Nor will reference be made to any disorders in which coagulation defects are the essential feature, since the latter are discussed in another article. Greatest attention will be given: (a) to anaphylactoid purpura, a disease wherein vessels are primarily damaged; and (b) to thrombocytopenic purpura, in which vascular damage is due in large part to lack of availability of platelet factors necessary for maintenance of vascular integrity.

Therapy of any disorder may be either rational or empiric, and the management of the purpuric patient entails both approaches. Well-defined physiologic principles form the basis for certain measures. Thoughtful speculation has led to other means of treatment. But to neither logic nor wisdom can be credited the merit of some clinically valuable agents. Although established means of therapy are few in number, there is nevertheless opportunity for discrimination in selection of regimens. Unfortunately, however, treatment consists too often in recourse to a haphazard array of agents considered by the attending physician to possess hemostatic effects.

The routine administration of vitamin K is wasteful, of flavenoids useless, and of calcium deplorable. Any value of estrogens is not established. Ascorbic acid has clearly documented effectiveness but only in scurvy. Transfusions of whole blood are indicated for replacement of blood loss. Other measures are best considered within the framework of each disorder under discussion.

THROMBOCYTOPENIC PURPURA

Pathologic Physiology.—The number of circulating platelets is a function of the balance between their rates of production and destruction. Little is known

about factors which regulate platelet production. Vitamins C, B_{12}, and folic acid are necessary. Hormonal effects are thought to be of importance. As will be discussed later, the presence of a plasma thrombocytopoietic factor has been suspected although not defined. The life span of platelets under normal circumstances is 7 to 10 days.[1] Breakdown from senescence and random destruction apparently takes place intravascularly and in the splenic sinusoids, the only area accessible to the platelet which may be extravascular. Compensation for an

TABLE I. CAUSES OF PURPURA

- Extravascular Factors
  - Congenital and familial
    1. Ehlers-Danlos syndrome
    2. Hereditary hypoplasia of the mesenchyme
  - Acquired
    1. Atrophic: cachexia, senile purpura
    2. Metabolic: Cushing's syndrome
- Vascular Factors
  - Congenital
    1. Vascular pseudohemophilia
    2. Hereditary hemorrhagic telangiectasia
  - Acquired
    1. Traumatic: purpura factitia
    2. Mechanical: orthostatic purpura
    3. Nutritional: scurvy
    4. Infectious: embolic, toxic, purpura fulminans
    5. Neoplastic: tumor emboli
    6. Metabolic: diabetes, uremia, (?) excess circulating histamine, vascular spiders in liver disease, pregnancy, etc.
    7. Associated with other vascular disease: hypertension, arteriosclerosis, polyarteritis and hypersensitivity angitis, other forms of vasculitis, amyloidosis.
    8. Immunologic: Schönlein-Henoch purpura, serum sickness, drug sensitivity, associated with autosensitization to erythrocyte stroma
    9. Dysproteinemic: cryoglobulinemia, macroglobulinemia, hyperglobulinemia
    10. Toxic: venoms
    11. Unknown: devil's pinches, purpura simplex
- Intravascular Factors
  - Platelets
    - Congenital
      - Qualitative: hereditary thrombocytasthenia
      - Quantitative: thrombocytopathic thrombocytopenia
    - Acquired
      - Qualitative: acquired thrombocytasthenia
      - Quantitative: thrombocytopenia (Table II)
- Coagulation Factors
  - Congenital or acquired deficiencies of synthesis
  - Acquired circulating anticoagulants
  - Acquired proteolytic crises: "fibrinolytic purpura"
  - Acquired intravascular defibrination
- Dermatologic Disorders
  - Purpura annularis telangiectoides, angioma serpingiosum, Schamberg's progressive pigmentary dermatitis, pigmented purpuric lichenoid dermatitis

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increase in turnover is possible under optimal conditions. Studies on human battle casualties who have experienced massive loss of blood[2] and on dogs following thrombocytopheresis[3] have revealed that loss of circulating platelets can induce within a few days a relative refractoriness to subsequent insults capable of lowering platelet levels in unprepared subjects. The production mechanism has been put in high gear by the demands. Destruction may outstrip production, however, with resultant thrombocytopenia. Although prompt and impressive remissions may be achieved by partial correction of excessive breakdown if the marrow is sound, the converse does not obtain; compensation for subnormal production is not possible because platelet life span cannot be prolonged.

TABLE II. CAUSES OF THROMBOCYTOPENIA

Decreased production of platelets

1. Replacement of bone marrow:
   Leukemia, carcinoma, sarcoma, lymphoma, granuloma, lipoidosis, sclerosis, fibrosis
2. Aplasia:
   Due to known causes: chemicals, drugs, radiation, oncolytic agents (Table IV), idiopathic
3. Deficiency diseases: megaloblastic anemias, scurvy
4. Some instances of idiopathic thrombocytopenia*
5. Splenomegaly of any cause (?)
6. Uremia (?)
7. Viremia, bacteremia (acute phase) (?)

Increased destruction of platelets

1. Splenomegaly
2. Stagnation of blood flow: extensive hemangioma, congestive heart failure, hypothermia
3. Thrombotic thrombocytopenia
4. Incompatible transfusion reactions
5. Massive blood loss with replacement with bank blood
6. Autoantibodies for platelets: most instances of idiopathic thrombocytopenia,* sensitization to certain drugs (Table III); associated with certain diseases: lupus erythematosus, some instances of chronic leukemia, some carcinomas, infectious mononucleosis; convalescent phase of acute exanthemata (?)
7. Accelerated intravascular coagulation: obstetrical accidents: amniotic fluid embolism, premature separation of the placenta; eclampsia (?)
8. Viremia, bacteremia (acute phase)
9. Thrombocytopathic thrombocytopenia
10. Uremia (?)
11. Onyalai (?)

*Note that idiopathic thrombocytopenia is considered in some instances to be due to deficient production and in other instances to accelerated destruction of circulating platelets.

Accelerated destruction may be caused by bacteremia or viremia, splenomegaly, autoantibodies, and thrombotic thrombocytopenia. Decreased production may reflect marrow replacement or aplasia, inadequate differentiation of megakaryocytes, and possibly splenic inhibition of marrow activity. A more detailed enumeration of etiologies of thrombocytopenia is given in Table II. Equilibrium may be further compromised if other handicaps are superimposed. For example, azotemia or localized infection may cause relapses of purpura in patients whose platelet balance is already in jeopardy from accelerated thrombocytolysis or impaired potential for production.

TABLE III. RELATIONSHIPS OF EXOGENOUS AGENTS TO THROMBOCYTOPENIC PURPURA OF AUTOIMMUNE TYPE*

AGENTS	DEFINITE	PROBABLE	POSSIBLE
I. Sedatives, analgesics, and antipyretics	Carbamides: allyl-isopropylacetyl carbamide (Sedormid), ethyl-allyl-acetyl carbamide	Phenylbutazone (Butazolidine)	Hydantoins: diphenyl hydantoin (Dilantin), phenylethylhydantoin (Nirvanol)
		Paramethadione (Paradione)	Procaine
	Barbiturates: phenobarbital, allyl-isopropyl-barbituric acid (Alurate), 5–(2 bromoallyl) 1-methyl 5 isopropyl-barbituric acid (Narcodorm)		Sodium salicylate
	Pyrazolon derivatives; amino-pyrine (Pyramidone), phenyldimethyl-isopropyl-pyrazolon Quinine Methylparafynol (Dormison)		
II. Antibiotics	Sulfonamides: sulfanilamide, sulfathiozole, sulfapyridine, sulfadiazine, sulfamezathine, amino-p-toluene sulfonamide, sulfisoxazole Arsenobenzols: arsphenamine, neoarsphenamine, sulfarsphenamine, silver arsphenamine, mapharsen, bismarsen Para-aminosalicylic acid	Streptomycin Isonicotinic acid hydrazide	Penicillin
III. Agents employed in cardiovascular diseases	Digitoxin Quinidine	Diamox	Tetraethylammonium chloride
IV. Heavy metals		Gold Silver Bismuth	

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V. Antihistaminics	Chlorprophenpyridamine (Chlortrimeton Maleate) 2-(N-phenyl-N-benzylamino-methyl)-imidazoline (Antazoline) Diphenhydramine hydrochloride (Benadryl)		
VI. Agents which influence endocrinologic processes		Iodides Thiourea derivatives thiouracil, propyl-thiouracil	Insulin Estrogens
VII. Foods		Foods: milk, potato, wheat, corn, eggs, citrus fruits, anchovies	
VIII. Miscellaneous	Dichlorodiphenyl-trichloroethane (DDT) Chrysarobin	Tetraethylthiuram disulfide (Antabuse) Viscum album, mistletoe berries	Leg stocking dye Insect bites Ergot

*These exogenous agents are considered to be responsible for certain instances of autoimmune thrombocytopenia. These instances are featured by an abundance of megakaryocytes in the marrow and are to be distinguished from exogenous causes for aplasia of the marrow. An attempt has been made to group the agents according to the plausibility of the evidence relating them to the development of the purpura.

In brief, the hemostatic equilibrium in any patient with either decreased production or increased destruction of platelets is delicately poised and subject to abrupt improvement or deterioration.

In most cases, thrombocytopenia is a manifestation of underlying disease (Table II). Therapy accordingly varies, but a discussion of criteria for selection of regimens in each instance will not be undertaken because of limitations of space.

Two comments are in order, however. First, idiopathic thrombocytopenia may be subdivided into immunologic and nonimmunologic varieties.[4] The former is considered to be due to excess destruction of platelets by autoantibodies and the latter to unknown mechanisms; insufficient production appears to be of fundamental importance in some instances. Second, careful clinical study is of paramount importance. Differentiation of the idiopathic disorder from thrombocytopenia due to other causes depends largely on thoroughness of verbal examination. Minute probing for history of exposure to drugs or other responsible exogenous agents is indispensable because a variety of substances (Table III) may complex with platelets thereby forming an antigen to which the host may react by producing an antibody.[5,6] As little as 0.5 mg. of an offending agent can then precipitate purpura in a susceptible individual. Certain causative agents are widely used; for example, quinine may serve as drug, flavor, or nostrum and is widely consumed in patent medicines and beverages. Thrombocytopenia is also a feature of marrow hypoplasia and aplasia, syndromes generally characterized in addition by leukopenia and anemia. Recognizable causes are listed in Table IV.

General Comments on Therapeutic Measures.—Four therapeutic measures are worthy of discussion in the present review: splenectomy, administration of adrenocortical steroids, platelet transfusions, and transfusions of plasma from donors with thrombocytosis.

Splenectomy: The best-evaluated measure is splenectomy, a procedure with merit for two reasons: (1) The spleen is the site most capable of removing damaged, though physiologically useful, platelets from the circulation.[4] (2) The spleen produces antibody; platelet antibodies have been demonstrated in higher titer in the splenic than the peripheral venous serum when both were simultaneously sampled.[4] This role is of secondary importance.

An additional possible effect of the spleen on platelets should be mentioned although it has not been established: the spleen may by unknown means inhibit proliferation of megakaryocytes or their ultimate cytoplasmic fragmentation into platelets. This concept has been advanced for two reasons: (a) the analogy to the clearly defined inhibition of erythropoiesis by the spleen in some instances of anemia,[7] and (b) the fact that megakaryocytes following splenectomy for thrombocytopenia seem to be morphologically more active in platelet production.[8]

Beneficial effects of splenectomy are usually rapidly evident. In instances of favorable response, bleeding promptly ceases and the platelet count usually increases within a few hours or, at the latest, within a few days. However, the reported experience of the results of splenectomy vary so much that many physicians are understandably confused. Some clinics report that all patients respond well while others consider that the procedure should be used only rarely because of both poor initial response and frequent late recurrence of thrombocytopenia

after splenectomy. A middle ground is the more common experience. The results obtained in the author's clinic will be reviewed later under "idiopathic thrombocytopenic purpura" where recommendations will also be given for the selection of those patients on whom splenectomy should be done.

TABLE IV. EXOGENOUS CAUSES FOR BONE MARROW APLASIA*

I. Agents which regularly induce aplasia if exposure is sufficient:
   1. Therapeutic agents:
      (a) Oncolytic compounds: nitrogen mustard and related compounds, urethane, Myleran, antimetabolites (folic acid antagonists, 6-mercaptopurine, etc.)
      (b) Ionizing radiation: roentgen rays, radioisotopes
   2. Occupational Hazards:
      (a) Chemical: benzol, mustard gas
      (b) Ionizing radiation: roentgen rays, radioisotopes

II. Agents occasionally associated with marrow aplasia:
   1. Therapeutic agents:
      (a) Antimicrobials: arsenobenzols (arsphenamine and its analogues, thiocarbasone, etc.), chloramphenicol, sulfonamides, quinacine, streptomycin, *oxytetracycline(?),* chlortetracycline(?),* para-aminosalicylic acid(?)*
      (b) Anticonvulsants: methylphenylethylhydantoin, methylphenylhydantoin, diphenylhydantoin,* trimethadione, paramethadione, atrolactamide, phenacemide
      (c) Antithyroid drugs: carbethoxythiomethylglyoxaline,* methylmercaptoimidazole
      (d) Antihistaminics: Pyribenzamine,* phenindamine*
      (e) Tranquilizers: promazine(?),* chlorpromazine*
      (f) Analgesics: phenylbutazone*
      (g) Heavy metals: arsenic, gold, bismuth,* silver,* mercury*
      (h) Miscellaneous: Amphetamine(?),* carbutamide*
   2. Occupational hazards:
      (a) Heavy metals: arsenic, gold, bismuth,* silver,* mercury,* lead*
      (b) Hair dyes, stove and shoe polishes
      (c) Insecticides: dichlorodiphenyltrichloroethane,* hexachlorocyclohexane, toxaphene(?),* chlordane(?)*
      (d) Organic solvents: coal tar solvent naphtha, petroleum naphtha, gasoline,* kerosine* (all four have variable content of benzol), ethylene glycol monomethyl ether, toluene(?),* xylene(?),* carbon tetrachloride(?)*
      (e) Miscellaneous: dinitrophenol, trinitrotoluene, dinitrobenzene, methylisopropylbenezene.*

***Those identified by an asterisk (*) have been rarely incriminated; those followed by a question mark(?) have not been clearly implicated although the evidence is sufficiently suggestive to warrant their inclusion. Because of the cracking processes employed in petroleum fractionation, it is now difficult to be assured of the relative safety of domestic petroleum as contrasted to coal distillate; benzol may be present in either product. It is also to be anticipated that additional agents currently undergoing clinical trial (e.g., tolbutamide acetazoleamide, etc.) may ultimately be added to the list.**

The risks of splenectomy are often overemphasized. Surgical casualties in past years are frequently included in current appraisals. Present day mortality is low, however; in the experience cited in Table V, 110 successive patients with idiopathic thrombocytopenia have required splenectomy; in this group there have been no surgical deaths. One patient was 89 years of age and several were only slightly younger. Surgical mortality is higher when thrombocytopenia is merely a facet of an underlying disease. Two of ten patients with symptomatic throm-

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bocytopenia died shortly following surgery. One man with chronic lymphocytic leukemia had intracranial bleeding for which emergency splenectomy was performed. He died in coma immediately after splenectomy was accomplished. A second patient, with carcinomatosis and extensive involvement of the liver, died of hepatic necrosis a few days postoperatively. In this single instance, surgical intervention seemingly contributed to the fatality.

An increased incidence of serious infections as a remote consequence of splenectomy in children has been suspected.[9] There is no unanimity of opinion on this point among pediatricians. Hematologists whose practice is limited chiefly to adults do not generally believe that there is a greater number of remote infections in their splenectomized population.

TABLE V. INCIDENCE OF DEMONSTRABLE PLATELET AGGLUTININS IN 201 PATIENTS WITH IDIOPATHIC THROMBOCYTOPENIA; RESPONSE TO SPLENECTOMY

A.	Agglutinins present in 153 patients (76 per cent). Splenectomized: 87 patients Response to splenectomy: 72 patients (83 per cent)
B.	Agglutinins not demonstrated in 48 patients (24 per cent). Splenectomized: 23 patients Response to splenectomy: 5 patients (22 per cent)

Adrenocortical steroids: ACTH, cortisone, hydrocortisone, prednisone, and prednisolone produce similar hematologic effects. Three desirable responses are possible: (1) An improvement in capillary fragility may be observed independent of an increase in platelet level and irrespective of the cause of the thrombocytopenia.[10] (2) Elaboration of platelet antibodies may be inhibited.[4] (3) Rate of formation of platelets may be enhanced.[11]

Evidence for the first two effects is substantial, whereas for the third role conclusive information is not available although suggestive data have been derived from clinical observations. Patients whose thrombocytopenia has been attributed, though only by exclusion, to impaired thrombocytopoiesis on the part of numerically adequate megakaryocytes have in isolated instances appeared to respond to large quantities of steroids.

Choice of agent varies. Currently prednisone and prednisolone are popular because of their more limited capacity for inducing sodium retention. The improvement in capillary fragility may be evident within several hours; the other effects generally require several days, if they occur at all in any given instance.

Platelet transfusions: Platelet viability is vulnerable to storage of blood for even a few hours. Ethylene diamine tetraacetic acid, disodium salt, is the best anticoagulant for platelet preservation,[12] or direct transfusions with nonwettable equipment may be employed.[13] Under optimal conditions the transfused platelets survive for only a week but a formidable variety of adversities can shorten the time to a negligible value. Minor breaks in technique of venesection in the donor can activate coagulation, thereby damaging platelets, or defects in technique of transfusion can lead to local deposition of a sizable portion of the administered platelets. Splenomegaly usually is associated with a shortened platelet life span. Platelet isoantibodies or antoantibodies in the recipient's plasma cause rapid breakdown of these elements.

Even more discouraging is the prospect that if optimal transfusions are accomplished, the survival times of subsequently transfused platelets in the recipient will very often become progressively shorter. Isoimmunity develops and, since the clinically important platelet antigens do not correspond to those in the erythrocyte, suitable grouping sera are not available which would permit selection of platelet-compatible donors.

Accordingly, at present, transfusions of viable platelets have real value only when (1) conditions for their survival are satisfactory, and (2) the anticipated need for this therapy does not exceed a few weeks in duration. Because of the difficulties in achieving significant long-term aid from transfusions of viable platelets, substitute approaches have been attempted. Nonviable platelet concentrates have been used.[14] Platelet and other tissue extracts have been evaluated. These two approaches are under continuing investigation; to date, the fleeting benefit obtained has required frequent doses of the material under study and no long-term data are available.

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Although the term "platelet transfusion" is appealing because it implies replacement therapy as a panacea for all varieties of thrombocytopenia, the procedure has very limited application. Less than 5 per cent of patients with thrombocytopenia of all varieties are suitable candidates for this therapy. The manifestations of thrombocytopenia can often be controlled by steroids, thereby decreasing the need. In addition, the indiscriminate use of platelet transfusions leads to isoimmunization in advance of the time when this replacement therapy might be most useful.

The desirability of continued efforts to achieve more useful substitution or replacement therapy for thrombocytopenia is evident.

Transfusions of plasma from donors with thrombocytosis: In a few instances there has been observed a response of thrombocytopenia to plasma from donors with high platelet counts, notably from individuals with polycythemia vera, chronic myelocytic leukemia, or essential thrombocytosis. It is entirely reasonable to assume that some steps in platelet production are under humoral regulation. Evidence is accumulating that thrombocytopenia may occasionally result from decreased endogenous availability of this humoral thrombocytopoietic factor and that the plasma of patients with overactive thrombocytopoiesis may contain an excess of the factor.[11,15,16] There are data, furthermore, which suggest that the material is distinct from gamma globulin and fibrinogen and is present in excess also in the plasmas of patients with autoimmune thrombocytopenia.[17]

Although assessment of the usefulness of infusion of plasma from donors with overactive platelet production is still in an experimental stage and has been studied in only an occasional subject, the theoretical implication of these observations is of great importance. The number of patients who might respond to more potent preparations could be sizable.

Selection of Specific Therapeutic Regimens.—Appropriate therapy requires accuracy of diagnosis. But thrombocytopenic purpura in its fully developed form is a medical emergency not suited to extensive or time-consuming diagnostic work-up prior to institution of treatment. Only patients with the mildest mani-

festations should be evaluated on an outpatient basis; all others should be hospitalized and the following immediately undertaken:

1. Detailed clinical work-up and competent hematologic investigation of the peripheral blood and bone marrow. The magnitude of the differential diagnosis is indicated in Tables II, III, and IV. The diagnosis of idiopathic thrombocytopenia is arrived at by exclusion and is less and less frequently made as the number of recognizable underlying causes increases. Certain features are nonetheless characteristic: the general well-being of the patient exclusive of the consequences of bleeding externally or in various sites, the lack of physical abnormalities other than those related to purpura per se, the absence of a palpable spleen, and the presence in the marrow of an abundance of megakaryocytes which appear to be deficient in platelet formation. In all instances examination of peripheral blood for leukemic cells or other diagnostic changes is mandatory. Similarly, the status of megakaryocytes and the presence of pathologic processes in the marrow must be appraised.

2. Typing and cross-matching of red cells, with whole blood maintained on reserve in the blood bank if not required at the moment for replacement of losses due to hemorrhage. For this purpose, fresh or specially collected blood has no added virtue.

3. Removal from contact with all chemicals, drugs, and cosmetics.

4. Administration of prednisone or prednisolone in a daily dosage of 50 to 100 mg. unless emergency splenectomy is performed.

The limited usefulness of platelet transfusions has been discussed; their chief value lies in the maintenance of a patient seriously affected with transitory marrow aplasia and purpura refractory to steroidal therapy. Plasma from donors with thrombocytosis has chiefly academic value at present. Beyond treatment of underlying diseases, therefore, the choice of regimen generally lies between splenectomy or use of steroids. Consideration of these two measures in the management of idiopathic thrombocytopenia will serve as a framework for their application to treatment of the secondary disorders.

Idiopathic thrombocytopenia: In the selection of therapeutic regimens in idiopathic thrombocytopenia both clinical and physiologic criteria have been employed. In some clinics the age of the patient plus the severity and the duration of his disease are regarded as the sole determining factors, while in our clinic the presence or absence of agglutinins for platelets in the serum is regarded as an additional and valuable guide.

There is general agreement that children, despite their irrepressibility, tolerate thrombocytopenia better than do adults. Furthermore, spontaneous recovery is more common in the younger than in the older age group. Therefore, pediatric hematologists reluctantly advise splenectomy. If evidence for an increased incidence of remote infections in splenectomized children can be confirmed, there should be even greater reluctance to have splenectomy done in this age group. Accordingly, therapy with steroids is almost uniformly the treatment of choice for children. However, if purpura persists beyond six months, splenectomy is commonly recommended. It seems reasonable to conclude that in childhood splenectomy for idiopathic thrombocytopenia is a procedure of second choice, to be employed early in the disease only in extreme circumstances

(e.g., unrelenting blood loss despite steroids or severe purpura with contraindication for steroid administration).

For therapy of idiopathic thrombocytopenia in adults, there is no similar general agreement. Before the advent of steroidal therapy, splenectomy was the sole clearly useful measure; but in the past few years the merits of hormonal management have been demonstrated. Some hematologists now teach that splenectomy is an obsolete procedure; to these men selection of a therapeutic regimen is therefore simple and steroids are given. However, the majority of investigators still feel compelled to discriminate between the candidates most appropriate for surgical and those best suited to medical therapy.

Some propose as a clinical guide that the disease be divided into acute and chronic forms.[18] Acute cases are treated medically, and splenectomy, when done at all, is reserved for chronic cases. Presumably the latter will ultimately require splenectomy because of self-perpetuating mechanisms which would induce relapse when steroids are discontinued even though remission accompanied their administration. But the clinical subdivision is usually not readily made; purpura is most often an alarming symptom and one which leads the patient to seek medical advice shortly after its development. Therefore, most patients have acute thrombocytopenia when first seen by their physicians. Prediction of its ultimate duration is not possible, although most instances in adults, if untreated, run a chronic or relapsing course.

Accordingly, other means of selection are desirable, and to this end an attempt at physiologic classification has been made. Idiopathic thrombocytopenia has been subdivided into *immunologic* and *nonimmunologic* varieties on the basis of presence or absence of agglutinins for platelets in the patient's serum (Table V). The percentage of cases included in the two categories varies greatly in different laboratories because of differences in technique of demonstrating platelet agglutinins, the difficulties and inadequacies of all current procedures for serologic study of the platelet, and the frequency of positive reactions in disorders featured by derangements of serum globulins. The author cannot compare his own experience with that of others, therefore, and can only present his personal observations while stressing that they are at variance with the results of studies made elsewhere.[19]

In three-fourths of our patients, platelet agglutinins have been demonstrated. Neither age nor sex nor duration of the patient's disease have influenced the percentage of positive results obtained. There is indicated in Table V an impressive correlation between the presence or absence of agglutinins and the patient's response to splenectomy. Whereas 4 out of 5 patients with demonstrable agglutinins in their sera respond to surgery, only one-fifth of those without antibody for platelets are similarly benefited. It would appear, therefore, that an additional criterion may be employed for the selection of candidates for splenectomy. General agreement on this matter will not be achieved until the technique for demonstrating platelet agglutinins can be simplified, standardized, and made more precise.

The author believes that both clinical appraisal and serologic results should be utilized. The following is the formulation employed:

1. If mucocutaneous and other bleeding is severe, splenectomy is carried out immediately. Similarly, intracranial bleeding, irrespective of other manifestations, is considered indication for emergency surgery. Admittedly, the most meticulous observation has limitations; sudden and fatal bleeding may take place in patients who have mild or minimal overt manifestations of their thrombocytopenia while other individuals with more profound signs may have no serious consequences even over a period of several years. Nevertheless, a reasonably useful correlation exists between the clinical picture and the dangers at the moment.

2. If purpura is less pronounced, steroids are administered and studies for platelet agglutinins are undertaken.

a. If platelet agglutinins are demonstrable and no platelet response to steroids has occurred after one week, the dosage is doubled or tripled for an additional week. If thrombocytopenia persists, splenectomy is then performed. But if the platelet level has increased, medical therapy is continued until a normal count has been achieved, whereupon steroids are gradually discontinued; if relapse follows, splenectomy is carried out. Alternatively, if only a small maintenance dose of steroids is required to perpetuate remission, splenectomy may be deferred, dependent on the patient's proximity to a competent surgical service should emergency operation be required and on his economic status. The cost of protracted medical therapy is greater than that of surgery in most instances especially when coupled with the fact that in the experience herein cited, splenectomy has been ultimately warranted in most adults. The use of steroids, furthermore, is not without inherent dangers.

b. If no platelet agglutinins are demonstrable and no response to steroids is evident even on increased dosage, the regimen is nevertheless continued, since subjects in this group are less responsive to splenectomy. However, surgery is ultimately warranted in many instances because of failure of response to medical therapy, complications from steroids, or the need for a prohibitively high dosage to sustain a remission.

If the manifestations mentioned in number 1 supervene at any time during medical therapy, emergency surgery may be recommended.

It should be reasserted that all criteria are fallible in a significant number of patients. Approximately 5 per cent of individuals are in no sense benefited by any combination of currently available measures, another 20 per cent receive only incomplete though variable degrees of improvement, and of the 75 per cent in whom lasting remissions are achieved, one quarter would have experienced spontaneous recovery. Accurate analyses of relative effects of therapy is therefore not possible, but it is estimated that splenectomy has been of lasting value to patients at least twice as frequently as has the use of steroids. Lasting value is herein defined as complete remission without subsequent relapse to the present; periods of follow-up range up to 6 years. Only 3 patients in the experience cited have died of causes related to idiopathic thrombocytopenia; all had failed to respond to either surgery or steroids. Two additional individuals have mild neurologic defects consequent to intracranial hemorrhage which immediately preceded surgery; both were on therapy with steroids at the time of their intra-

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cranial bleeding. One patient who failed to respond to splenectomy or steroids has had one episode of nonfatal cerebral bleeding.

Assays for platelet agglutinins are not generally available. In their absence, choice of candidates for splenectomy should be guided: (1) by the clinical criteria presented for the initial selection of emergency surgery versus medical therapy (vide supra), and (2) the adequacy of responsiveness of the purpura and thrombocytopenia to steroids over a 2- to 3-week period. It is the author's conviction that the greatest danger to the patient resides in the complacency of his physician; protracted trial with regimens which have failed to induce remission is to be decried irrespective of the number of criteria at hand for their selection.

In the group of patients in whom all conventional approaches have been unavailing, two additional procedures are worthy of consideration: extensive work-up for sensitivity to food allergens or other ubiquitous substances which might possibly be responsible, and search for accessory spleens. The first of these has only rarely been of merit, although its application has been limited. The second is dangerous in that short of blind exploration, Thorotrast studies are required and may of themselves lead to delayed but fatal toxic effects; therefore with the exception of the elderly or the most extremely intractable cases, use of Thorotrast should be discouraged. Furthermore, accessory splenectomy has rarely cured thrombocytopenia though the number of trials reported is very small.

As a final resort, transfusion of plasma from donors with thrombocytosis may, in a few cases, prove rewarding. This approach holds some promise for the future.

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TABLE VI. MATERNAL AUTOIMMUNIZATION TO PLATELETS AND NEONATAL THROMBOCYTOPENIA

Number of mothers with thrombocytopenia		13*
Number of infants born to these mothers		24
Number with neonatal thrombocytopenia	23	
Number without neonatal thrombocytopenia	1†	

*Eight splenectomized previously; 5 in complete remission, 2 in partial remission, 1 in relapse.
†Said to appear normal; no hematologic studies performed.

Thrombocytopenia in Pregnancy and in the Newborn.—Idiopathic or secondary thrombocytopenia may occur in a mother during pregnancy or in an infant during the neonatal period. Secondary forms will be considered in the next section. The idiopathic varieties in mothers may or may not be associated with autoantibodies for platelets. In the infant idiopathic thrombocytopenia may be due to placental transfer of maternal autoantibodies (i.e., reflecting disease in the mother), or of isoantibodies (the so-called primary idiopathic thrombocytopenia of the newborn, analogous to hemolytic disease of the newborn, and unaccompanied by evidences of maternal thrombocytopenia).

In general, management of the maternal disorder is as outlined for nonpregnant patients but may be modified by two considerations:

1. If the woman has autoimmune idiopathic thrombocytopenia, her infant will almost invariably be affected (Table VI). Similarly, if she had autoimmune

purpura relieved by splenectomy, the same correlation often obtains because of the frequent persistence of antibody despite clinical remission following splenec, tomy. In contrast, if the mother has nonimmunologic thrombocytopenic purpura- her baby's platelet level will be normal (Table VII).

TABLE VII. MATERNAL THROMBOCYTOPENIA WITHOUT PLATELET ANTIBODIES AND WITHOUT NEONATAL THROMBOCYTOPENIA

Number of mothers with thrombocytopenia		7
Number of infants born to these mothers		7
Number with neonatal thrombocytopenia	0	
Number without neonatal thrombocytopenia	7	

2. Either steroids or surgery endanger the fetus early in pregnancy; the first may induce congenital anomalies,[20] the second may precipitate abortion. The likelihood of adverse effects on the fetus from either measure diminishes later in pregnancy.

Accordingly, an effort is made to avoid usage of steroids during the first trimester of pregnancy and then to maintain the mother on these agents later until a viable infant may be expected. Thereupon if platelet antibodies were present initially, but a normal platelet level has been now achieved, the mother should be allowed to be delivered normally. If still thrombocytopenic, though free of purpura, she should receive an increased dosage of steroids in an effort to inhibit further antibody production and thereby protect the infant. But if thrombocytopenia and purpura persist, splenectomy and cesarian section may be undertaken. Lastly, in the patient previously splenectomized for autoimmune thrombocytopenia and now in remission, if agglutinins are still demonstrable, steroids may nevertheless be given to the mother to decrease elaboration of antibody which might gain access to the infant's circulation.

If platelet antibodies have not been demonstrated, splenectomy should be performed only if hemorrhagic manifestations are pronounced despite steroidal therapy, since for reasons unknown remission may occur following delivery.

In no instance herein cited has there occurred either a death or residual damage in the mother from the coexistence of thrombocytopenia and pregnancy.

Infants recover spontaneously from neonatal thrombocytopenia over a period of 1 to 2 weeks to 4 to 5 months. The time of greatest danger is the period of actual birth and the few days immediately thereafter. The most important measure from the infant's standpoint, therefore, is anticipation of the disorder and precautions to minimize birth trauma; the prognosis otherwise in the infant is good and may be improved with steroids. It is possible to predict the development of neonatal thrombocytopenia in infants born to mothers with autoimmune thrombocytopenia or a history of purpura corrected by splenectomy, or a history of giving birth to infants who developed neonatal purpura. In the absence of a history of previous episodes, the isoimmune form of thrombocytopenia in the newborn cannot be anticipated.

If foreseen, some of the dangers of neonatal purpura may be averted by special care on the part of the obstetrician. Of particular importance is avoidance

of instrumentation in delivery and ability and willingness to perform a delivery by section should it appear warranted. There have been no deaths nor residual effects in the experience with infants presented in Tables VI and VIII, when awareness of the dangers was known to the obstetrician. But 4 neonatal deaths occurred in 9 deliveries performed without forewarning.

Secondary Thrombocytopenia.—Steroids benefit the capillary defect, as in idiopathic thrombocytopenia, and therefore are widely employed. In addition,

TABLE VIII. MATERNAL ISOIMMUNIZATION TO PLATELETS AND NEONATAL THROMBOCYTOPENIA

Number of mothers (all clinically normal)		6
Number of infants born to these mothers		7
Number with neonatal thrombocytopenia	7	
Number without neonatal thrombocytopenia	0	

TABLE IX. OTHER THROMBOCYTOPENIC STATES FEATURED BY AUTOIMMUNIZATION TO PLATELETS*

Disseminated lupus erythematosus	8 out of 10 patients studied (6/6)
Chronic Lymphocytic leukemia	2 out of 3 patients studied (1/2)
Carcinoma	
Ovary,* colon,* and undetermined primary site,* one instance each; breast two instances	3* out of 5 patients studied (1/2)
Selective thrombocytopenia due to drugs	10 patients (0/0)
Quinine 4 instances, quinidine 4 instances, barbital derivatives and Benadryl one instance each	

Numbers in brackets represent (number of remissions induced by splenectomy / number splenectomized).

*Note that splenectomy has been commonly beneficial.

they may favorably alter the underlying disease as in lupus erythematosus and thereby improve the platelet level. In my experience if the bone marrow has been cellular with respect to megakaryocytes and the prognosis is otherwise reasonably good, criteria similar to those for idiopathic thrombocytopenia have been cautiously applied for selection of candidates for splenectomy. The greater number of variables has often influenced and led to deferral of the ultimate decision. Furthermore, positive agglutination reactions, presumably spurious, are common in sera of patients with distortions of their serum protein profiles.[21] When splenectomy has been undertaken, surgical techniques have varied, e.g., portacaval or splenorenal shunting procedures may be simultaneously performed if necessary for congestive splenomegaly, cirrhosis of the liver, or hemorrhage from esophageal varices.

Contraindications to splenectomy are more common in secondary thrombocytopenia; they require no comment here, except for reference to one admonition recently reported. It has been suggested that removal of the spleen exerts a deleterious effect on the course of lupus erythematosus. There has been no clear evidence of this in the experience with the six patients herein cited (Table IX).

The over-all responsiveness to therapy is understandably less in secondary thrombocytopenia and the ultimate prognosis more unpredictable than in patients whose purpura is of the idiopathic variety.

ANAPHYLACTOID PURPURA

A generalized angiitis with predilection for cutaneous, joint, gastrointestinal, and renal manifestations has been variously designated as acute or chronic vascular, Schönlein-Henoch, or anaphylactoid purpura. The disorder is most common in childhood and youth, and evidence has been adduced that autoantibodies against endothelium are responsible.[22,23] As in thrombocytopenia, a causal relationship to a number of exogenous agents has been postulated (Table X).

TABLE X. CAUSES OF ANAPHYLACTOID PURPURA*

Bacteria:	
	Especially streptococci: also tuberculosis and bacterial vaccines
Drugs:	
	Antibiotics: penicillin, streptomycin, sulfonamides, viomycin
	Antihistaminics
	Analgesics and antipyretics: pyramidon, salicylates, acetophenetidin, phenylbutazone
	Sedatives: barbiturates, chloral hydrate, neprobromate
	Antiepileptics: hydantoin, phenylethylhydantoin, meprobromate
	Heavy metals: gold, arsenic, mercury
	Agents employed in endocrinologic diseases: estrogens, insulin, thiouracil
	Miscellaneous: quinine, menthol, cinchophen, dinitrophenol, ipecac
Chemicals:	
	Coal tar derivatives (?)
Foods:	
	Wheat, egg, chocolate, milk, beans, tomatoes, potatoes, onions, strawberries, blackberries, plums, nuts, pork, chicken, fish, crab
Physical agents:	
	Cold
Other causes:	
	Insect bites, serum sickness

*The table is merely a guide since any agent to which history of exposure is elicited must be considered potentially responsible.

Management is therefore directed toward the suppression of formation of antibody. Two approaches have been employed. The classic technique is the interruption of exposure to the suspected responsible allergens.[24] In the instance of bacterial etiologies, antibiotics are indicated. The second means of therapy is the administration of adrenocortical steroids in dosages similar to those employed in thrombocytopenia.

Responsiveness to therapy is variable and unpredictable. In a few instances, impressive improvement has followed detection and removal of the causative agents.[25,26] Remissions coincident with administration of steroids have been documented.[27] Both measures have been clearly of merit in only a minority of instances in the author's experience. The benevolence of nature and time have

appeared more often to be of value. Until methods are available for dissecting apart the specific processes which are included under this diagnosis, anaphylactoid purpura will continue to be irregularly responsive to treatment.

The acute phase is attended with a significant though small mortality, and the chronic disorder is not always readily separable from other forms of vasculitis. Therefore the measures available should be tried.

OTHER VARIETIES OF PURPURA

In Table I are listed numerous other causes for purpura; most are reflections of underlying disease. Their management is primarily directed toward the inciting cause. The only available symptomatic measure worthy of trial in most instances is steroids, but all too often either contraindications or chronicity make their employment impractical.

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SUMMARY

Purpura is a physical sign featured in a variety of unrelated illnesses and is the ultimate reflection of a number of derangements of hemostasis. An attempt has been made to present briefly a schema for approach to treatment, with particular emphasis given to management of thrombocytopenia.

Beyond correction of underlying diseases, very few measures are available. Adrenocortical steroids are the most useful "broad-spectrum" therapy, but their application is largely limited to control of the manifestations of thrombocytopenia and anaphylactoid purpura. In thrombocytopenia, enthusiasm for hormonal management has propelled the therapeutic pendulum away from splenectomy as the measure of choice; however, surgery remains the ultimate means of remission in most adults with the idiopathic disorder and in many instances of the secondary variety. The concept that idiopathic thrombocytopenia purpura may be divided into immunologic and nonimmunologic types has been discussed. Approximately 80 per cent of patients with the immunologic variety respond favorably to splenectomy. In anaphylactoid and other nonthrombocytopenic purpuras attempts at symptomatic management with steroids alone are generally disappointing; the precipitating factors or underlying diseases are more vulnerable targets of therapy.

Despite the paucity of available therapeutic measures, the uncritical administration of any agents claimed to have a role in normal hemostasis or any influence on defective hemostasis can only be condemned. This approach, in lieu of accurate diagnosis and thoughtful appraisal, is virtually always ineffective and expensive and too often a contributor to fatal outcomes.

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THE THERAPY OF DISORDERS OF COAGULATION

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PROGRESS in the field of coagulation during the past two decades has been gratifying and at the same time bewildering. Where there was one hemophilia, there are now five. Where there was one form of "prothrombin" deficiency, there are now three. Where there were one or two conditions associated with fibrinogen lack, there are now a multitude.

It has been charged, and with some justification, that too often research in blood coagulation has been academic and neglectful of the practical application of knowledge.[1] The definition of a newly discovered coagulation factor is often not associated with a similar precise delineation of therapy for the unfortunate patient lacking the factor.[2] To the person who must assume the care of a bleeding patient, this attitude may be somewhat trying. But the other side of the coin would reveal physicians to be often neglectful of advances in coagulation which would be of benefit to their patient. It has been indicated that the time is now at hand for a better understanding of the various clotting defects and a more rational and specific approach to therapy.[3,4] In the following pages the physiologic basis for therapy in various coagulation disorders will be explored. The detailed clinical descriptions and means of laboratory identification of these disorders can be only briefly presented. Similarly the antecedent historical events and the actual discoveries (often simultaneously) of these conditions are quite beyond the scope of the paper and may be found elsewhere.[5,6]

GENERAL PRINCIPLES

Coagulation factors (with the exception of platelet thromboplastic factor which is probably a phospholipid[7]) are plasma proteins of extraordinary biologic activity. With the exception of fibrinogen, these substances exist in "trace" amounts[3] and yet exert a profound influence. An approximation of the activity of some of these proteins may be gained from a consideration of the fact that 1 mg. of purified human prothrombin, when activated, can clot 2,000 ml. of a standardized fibrinogen solution in 15 seconds.[8]

The distribution of these proteins in the body is largely unknown, but there is reason to believe that as with other plasma proteins[9] they are divided almost equally between the intravascular and extravascular spaces. Analysis of the

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disappearance curve of fibrinogen in a case of afibrinogenemia by Gitlin and Borges[10] would indicate such a distribution for fibrinogen, and Fantl and Sawers[11] have suggested that antihemophilic globulin (AHG) and plasma thromboplastin component circulate through a space two to three times the blood volume.

The production of plasma coagulation factors occurs through cellular processes that are as yet poorly understood. The materials from which these proteins are derived and the enzymatic steps involved are also unknown although for at least three coagulation factors[12,13] prothrombin, stable factor, and plasma thromboplastin component, a common vitamin, K, appears necessary. The mode of action of this vitamin has been suggested to be that of a coenzyme[14] in the hepatic processes leading to formation of the coagulation proteins. Whatever the basic nature of these processes, there is little question that they are under genetic conditioning. Hereditary deficiencies of almost every coagulation factor have been reported and the mode of inheritance has been fairly well defined. In hereditary antihemophilic globulin deficiency, the genetic conditioning not only determines which defect develops, but also the degree of the deficiency[15,16] and thereafter the constancy of the defect.[16] A similar genetic influence has been noted in hypoprothrombinemia[17] and undoubtedly occurs with respect to other factors as well.

The life span of most coagulation proteins is considerably shorter than that of other plasma proteins, antihemophilic globulin having a half-life of a few hours[18] and fibrinogen a few days.[10] Prothrombin disappears from the circulation in 36 to 72 hours and labile and stable factor in 12 to 28 hours.[19] More important than total life span of a coagulation factor is the time it takes for the concentration of a given coagulation factor to reach a critical level below which bleeding may occur. Although traces of antihemophilic globulin may persist for as long as 4 to 6 days[20] (Fig. 1), its effective concentration may last only 12 to 24 hours or less (Fig. 2). The rapid turnover of coagulation factors under physiologic conditions suggests either unusual mechanisms of destruction or, more likely, a constant rate of utilization through continuous in vivo clotting. The high turnover rate of prothrombin together with the finding of formed thrombin in the plasma[21] strongly suggests such a hypothesis. In addition to loss through utilization, coagulation factors may be depleted by blood loss, consumption during internal hemorrhage, or theoretically through the neutralizing or destructive action of antifactors (anticoagulants).

The various therapeutic approaches to a deficiency of a coagulation factor may now be examined. The modification of a genetically determined trait in inherited coagulation factor deficiencies is as yet unaccomplished. Replacement therapy remains the sole means of restoring coagulation factors in such cases. Therapy through the supplying of a deficient essential coenzyme is known only in vitamin K lack. Thus, prothrombin and stable factor deficiencies occurring because of vitamin K lack from whatever cause can be readily restored by vitamin K. Improvement in cellular function leading to the enhanced production of coagulation factors is limited to those instances of liver disease which respond to current hepatic regimes. Where liver damage is severe or even irreversible, replacement therapy must be utilized. Suppression of antifactors is

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theoretically possible in those states associated with various anticoagulants and fibrinolysins. Not infrequently, however, control is imperfect or lacking and replacement therapy must be employed. A minimum daily utilization of a coagulation factor must be expected. However, in those patients who are already deficient in a factor, any unusual increase in such loss whether through

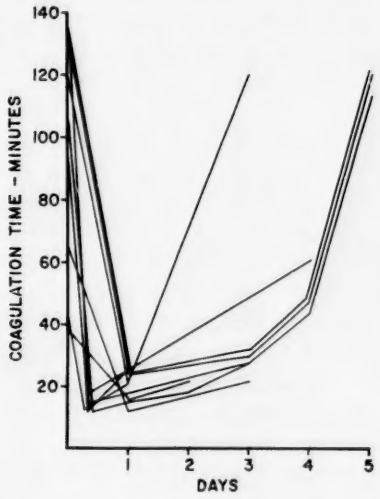

Fig. 1.—The effect of the infusion of fresh plasma in AHG deficiency. The coagulation time returns to base-line values in 5 days, indicating that traces of AHG last for 4 days.

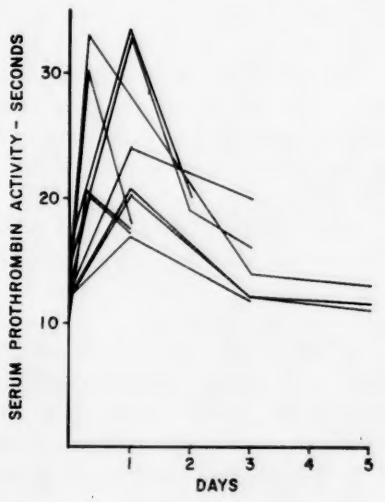

Fig. 2.—The effect of the infusion of fresh plasma in AHG deficiency. Serum prothrombin activity falls below the normal value of 21 seconds in 12 to 48 hours. Further persistance of AHG has little therapeutic effect.

external bleeding or internal consumption in a hemorrhagic area becomes important. In general such exaggerated loss is controlled by temporary replacement therapy leading to improved hemostasis and arrest of hemorrhage.

From the foregoing, the importance of replacement therapy in management of coagulation disorders is apparent. The intelligent use of such replacement therapy requires some knowledge of the properties of the factor or factors lacking. Of particular interest would be its storage stability, its reaction to various commonly used blood preservatives, its concentration and distribution in plasma and plasma fractions, its fate during coagulation, its critical concentration,* and its life span in vivo.

Intelligent use further requires some information concerning the patient in addition to the specific diagnosis (not often easily arrived at). Since the administered lacking factor is to be distributed in the intravascular space, an approximation of this derived from the patient's weight is useful. Similarly the extent of the deficiency in the patient's blood and the presence or absence of antifactors capable of neutralizing the infused factor are important. In the thromboplastin deficiencies these factors can be roughly assessed by the in vitro admixture of graded amounts of fresh plasma with the patient's whole blood and noting the extent of correction of the coagulation defect.[22]

The plasma requirements in any uncomplicated defect may be approximated by a formula as follows:

Body weight in kilograms $\times 10^3 \times 0.045$† $\times$ (critical concentration of deficient factor‡ minus patient's plasma concentration of deficient factor‡) = minimal amount of milliliters of plasma to be infused.

Since the patient's concentration is usually negligible, this may be eliminated from the formula.

Example 1. 70 Kg. male with AHG deficiency (classical hemophilia)
Normal plasma responsiveness (critical level of AHG 10 per cent of normal)
$70 \times 10^3 \times 0.045 \times 0.10 =$ minimal amount to be infused
315 ml. = minimal amount of plasma to be infused.

Since more than this amount is required to compensate for diffusion into tissue spaces and for blood loss, the requirement may be further raised to two or three times this amount.

Example 2. 60 Kg. female with afibrinogenemia and fibrinolysis
(critical level of fibrinogen 30 per cent of normal)
$60 \times 10^3 \times 0.045 \times 0.30 =$ minimal amount to be infused
810 ml. = minimal amount of plasma to be infused.

Since 810 ml. of plasma would be just adequate if there were no destruction of fibrinogen during the lengthy infusion, if there were no diffusion into the tissue spaces, and if there were no loss through hemorrhage, it is obvious that much larger amounts are usually required, and hence plasma may be impractical. Concentrated fibrinogen would best serve in this instance in amounts of at least 3 to 4 Gm. initially.

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*That concentration below which bleeding may be expected.
†Per cent of total body weight constituting plasma volume.
‡Expressed in per cent of normal.

SPECIFIC COAGULATION DEFICIENCIES

Plasma Thromboplastin Factor Deficiencies.—

Antihemophilic globulin: This substance is an euglobulin present in normal plasma and often associated with fibrinogen although distinct from it.[23] It is separated on fractionation with Cohn Fractions I, III, and III_2[24] although, practically, only Fraction I has been available for therapy. This fraction is said to contain only 35 per cent or less of the original plasma AHG content.[25] AHG is consumed during coagulation and is not detectable in serum.[26,27] It is not removed by barium sulphate or Al $(OH)_3$ adsorption and is precipitated by 33 per cent ammonium sulphate saturation almost quantitatively.

Antihemophilic globulin is peculiarly and unpredictably labile and may be largely inactivated even at refrigerator temperatures in 24 hours.[28] It has been shown however that such lability is greatly influenced by the anticoagulant used: citrate and heparin[29] tend to stabilize while oxalate tends to accelerate its disappearance.[6] The use of gravity collection and careful admixture of blood and anticoagulant also tends to preserve AHG. The widespread use of ACD solution as an anticoagulant, improved and speedy collection technique, and superior refrigeration equipment has to some extent modified previous concepts on the lability of antihemophilic globulin in banked blood. Recently, antihemophilic globulin has been found to last in banked blood as long as 14 days,[5] in full potency for 3 weeks,[3] and in equal potency with frozen fresh plasma for 2 weeks.[30] Frozen fresh plasma kept at −20° C. may preserve its AHG activity for many months although some loss does occur in the first 4 weeks.[30] Antihemophilic globulin may be preserved in a lyophylized state when processed from freshly drawn blood and dried without delay.[31] In this state it may exhibit anywhere from 50 per cent[30] to full potency,[31] figures which compare quite favorably to the variation in AHG content in fresh plasma[15] or frozen fresh plasma. The value of the comparative data cited above must be subjected to more extensive studies. All such work suffers from the inability to control the wide range of AHG content of normal plasma (from 50 to 150 per cent of an average norm) and also to control anti-AHG substances present to varying degrees in individual plasmas.[32] Until further data are available, fresh plasma or frozen fresh plasma is preferable to banked plasma in therapeutic attempts unless the latter is all that is available.

The effective life span of antihemophilic globulin in the circulation has already been alluded to and varies from 12 to 24 hours.

The stated critical level of AHG has varied widely according to the criterion of correction accepted by various authors. If clotting time normality is accepted as a definitive criterion, 5 per cent AHG is adequate. Ten to 20 per cent is generally accepted as being adequate for normality of coagulation time and prothrombin consumption[3,22] although Brinkhous states that 5 per cent or less AHG may give normal coagulation times and prothrombin consumption and still be inadequate to stop hemorrhage.[18] MacFarlane, Biggs, and Bidwell using the thromboplastin generation test as a measurement of adequate correction have set 30 per cent as a critical level.[33] Approximately 50 per cent has even been advocated, especially during surgery,[34] but since the latter value can only be achieved by a 50 per cent replacement, it seems impractical. A goal of 10 per cent to 20 per cent is practical and has generally proved effective, when achieved.

A word must be mentioned concerning purified concentrates containing antihemophilic globulin. Fraction I has a potency which is quite variable,[30] and which may be considerably less than the plasma from which it is derived. It does have the virtue of being concentrated so that a small volume of fluid is required for administration. However, its widespread use has been limited by its lack of uniform potency, its short supply, and its possible heightened antigenicity leading to the development of anticoagulants.[62] Furthermore the fractionation process tends to concentrate the hepatitis virus in the active material. This is of considerable concern since plasma pools are used as the initial source leading to possible extensive contamination. Of greater promise therapeutically is the concentration of purified bovine AHG 100 to 400 fold.[35a] Such material has been used and more than adequately substitutes for human AHG.[33] Unfortunately such concentrates have the property of agglutinating platelets and furthermore are highly antigenic. Thus only limited trials have been performed. More recently, a process of purifying and concentrating AHG from human plasma with an efficiency far in execss of the older method has been introduced.[35b] This may well lead to a renaissance of the use of AHG concentrates in the treatment of hemophilia.

Hereditary, congenital AHG deficiency (classical hemophilia, hemophilia A): This disorder is the commonest type of hemophilia, constituting approximately 80 per cent of hemophiliacs.[36,37] The defect is inherited as a sex-linked recessive and is permanent. The keystone of therapy is replacement of AHG through the intravenous infusion of fresh plasma, frozen fresh plasma, lyophilized fresh plasma or rarely Fraction I. The approximate dose of any plasma preparation for adults is 300 to 500 ml. repeated at 12- to 24-hour intervals. In particularly difficult cases, more frequent or even constant infusion may be necessary[20] although the danger of circulatory overload must be considered. Treatment should be instituted prior to any operative procedures, however slight, upon trauma even prior to objective signs of bleeding, and upon bleeding threatening to vital function or life. The size of a hemorrhage is of minor importance; the location is all important. Thus a subcutaneous hematoma need not be treated systemically whereas even the slightest presence of a bulge in the throat of a hemophiliac calls for intensive therapy (Fig. 3). Plasma therapy should be

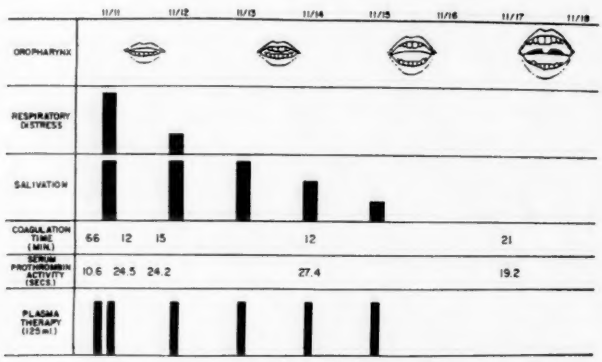

Fig. 3.—Therapy of hemophilic oropharyngeal bleeding. Constant maintenance of normal clotting times and serum prothrombin activity arrests the hemorrhage and permits prompt reabsorption of the hematoma.

continued for several days after a hemorrhage has subsided and fresh whole blood should be utilized in the therapeutic program as hemoglobin needs arise. The management of a bleeding hemophiliac from several viewpoints has been recently reported.[38] Several problems peculiar to hemophilia are worthy of mention. Hemarthroses are particularly troublesome and apt to be recurrent. Acute joint bleeding is regarded as a major bleeding episode and is treated with full plasma therapy, bed rest, and ice applied locally. Instillation of hyaluronidase,[39] hydrocortisone,[40] or other enzymes in joints preceded by plasma therapy and aspiration has been advocated. Such instillations have been found to retard healing,[41] and in our experience sometimes cause intensification of pain and renewed bleeding. They are not to be recommended. Routine simple aspiration can only be condemned and should be restricted solely to massively distended joints. Following arrest of hemorrhage, orthopedic rehabilitation may be required and necessitates traction, casts, and corrective braces. Details of such orthopedic management have been outlined by Jordan.[42] Hematuria is common,

recurrent, and often resistant to plasma therapy.[5] Vigorous plasma therapy may be followed by intracalyceal clotting with renal colic and urinary tract blockage. Therapy consists of supportive care, transfusion of whole blood if anemia becomes severe, and bed rest. If hematuria persists, a trial of plasma therapy should be attempted.

Surgery in a hemophiliac is still extremely hazardous despite improved plasma control.[43] Acute abdominal emergencies in a hemophiliac are more often bleeding episodes either into the gut wall, peritoneal cavity, or retroperitoneal space than inflammatory conditions. Plasma therapy, antibiotics, and intravenous fluids are indicated for a limited time, during which the true nature of the intra-abdominal process will either become apparent or the episode will subside. Recent fatalities in hemophilia have almost exclusively been limited to ill-advised surgery for conditions which have proved to be due to hemorrhage alone. Thus intelligent delay has much in its favor.

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"Sporadic" antihemophilic globulin deficiency: This condition refers to cases of true antihemophilic globulin lack appearing in females[44] without antecedent family history and only minor changes in other clotting proteins. In one family a male and female sibling were involved severely although another sibling was unequivocally normal as were the mother and father.[45] Therapy of this disorder is similar to that of hereditary antihemophilic globulin deficiency.

Vascular hemophilia (combined "pseudohemophilia" and antihemophilic globulin deficiency): This unusual association has been described by Alexander and Goldstein,[46] Schulman,[47] and others.[48-50] It consists of a true AHG lack and a vascular defect and is characterized by prolonged clotting time, impaired prothrombin consumption, low AHG assay, and prolonged bleeding time. Plasma therapy as in classical hemophilia corrects the coagulation defect but does not influence the vascular defect significantly. In view of the recent claims for the efficacy of steroid therapy in "pseudohemophilia,"[51,52] a combined approach should be tried.

Circulating anticoagulants (anti-AHG): These conditions represent a heterogenous group of clinical syndromes in which antithromboplastic factors are present. More recently with improved technique some of these anticoagulants have been demonstrated to show a high order of specificity either against AHG[53-55] or against PTC.[54-57] An excellent review of the subject has been presented by Hougie.[58] The background of hemophilia, pregnancy,[59] transfusions, and collagen disorders[60] that accompany these states has repeatedly suggested an immunologic etiology analagous to blood group sensitization and has even led to the term "autoimmune hemophilia."[61] This immunologic theory has received strong support from the demonstration of precipitins to antihemophilic globulin in refractory hemophiliacs,[62] a finding which has recently been questioned.[63] Therapy with plasma is often ineffective even with virtual[59] or actual exchange transfusion[38] although transient effects on the coagulation time may be seen.[62] Steroid suppression of the anticoagulant has now been tried many times[38,54,58,60] and has been successful in only one reported instance.[64] Withholding of blood or plasma is said to be followed after a variable interval by disappearance of the anticoagulant but this may be difficult to do if active bleeding supervenes.

Fraction I has failed although the advent of high potency concentrates of AHG may prove to be effective in overcoming anticoagulant action.

AHG lack with hypofibrinogenemia: This deficiency is part of the complex multiple coagulation failure associated with afibrinogenemias of pregnancy or that associated with carcinoma of the prostate.[6] We have observed AHG to be present in only trace amounts during acute afibrinogenemia secondary to abruptio placenta. PTC was unaffected.

The therapy of this disorder is that of the underlying conditions supplemented by fresh whole blood rather than bank blood to restore AHG levels (see below).

Plasma thromboplastin component factor: This factor described by Aggeler and his co-workers,[65,66] is found in normal plasma in association with the beta$_2$ globulin[68] fraction of plasma and serum and is precipitated by 33 to 50 per cent ammonium sulphate saturation. It is present in both plasma and serum, possibly in large amounts in the latter, is adsorbed by barium sulphate and aluminum hydroxide, and can be eluted by sodium citrate. Plasma thromboplastin component is not found in Fraction I but is found in Fractions III and IV. It is stable on storage for many days to weeks and is found in AHG-deficient plasma. Aggeler and his co-workers have concentrated PTC by barium sulphate adsorption, citrate elution, and ethanol purification to an extent of 15 times by in vitro testing.[65] The life span of this factor has been estimated to be 2 to 3 weeks[66,69] as judged by the clotting time, to 72 hours[70] as judged by the effect on prothrombin consumption. It does appear to have a somewhat longer survival than antihemophilic globulin although this may be due to its higher content in plasma than AHG.[69]

The critical level of plasma thromboplastin component has not been established although it is probably close to that of antihemophilic globulin.

An unusual aspect of plasma thromboplastin component is its dependence on adequate levels of vitamin K for its formation.[13,71] In this respect, it is closely allied to prothrombin and stable factor, with which it shares other characteristics as well.

Hereditary plasma thromboplastin component deficiency (hemophilia B, Christmas disease): This disorder, discovered almost simultaneously[65,72,73] by several groups, is now known to constitute about 15 per cent of the patients considered to have hemophilia. It is inherited as a sex-linked recessive, has varying degrees of severity, and clinically is identical with classical hemophilia. Because of the stability of the deficient factor and its distribution in plasma fractions other than Fraction I, its therapy is somewhat different from that of classical hemophilia. Fresh plasma need not be used. Ordinary banked plasma is quite adequate for treatment (possibly superior to fresh plasma) as is serum.[66,70] Fraction I is useless and as yet no concentrates other than experimental ones are available for therapy. Since the critical level appears to be similar to that of AHG, comparable amounts of plasma must be given to effect a response although intervals between administration may be lengthened to 24 to 48 hours due to the longer survival of PTC. Traces of PTC may persist for days but in amounts inadequate for hemostasis. Details of management are identical to that of classical hemophilia.

Circulating anticoagulants (anti-PTC): This condition has been reported only in patients with PTC deficiency and is treated in a manner analagous to that for other antithromboplastin factors.

Plasma thromboplastin component deficiency associated with vitamin K lack: This condition is always associated with prothrombin deficiency and responds to vitamin K.

Plasma thromboplastin antecedent factor (PTA): This factor described by Rosenthal, Dreskin, and Rosenthal[74,75] is a beta$_2$ globulin found in Cohn Fraction III and IV$_1$ and is essential for plasma thromboplastin formation. It is present in normal plasma and serum and cannot be readily adsorbed with barium sulphate although traces can be eluted from the adsorbant by citrate. It is not found in Fraction I. It is very stable on storage and may be fractionated by 25 to 33 per cent ammonium sulphate saturation.

The critical in vitro level for the complete correction of coagulation time and prothrombin consumption in four patients was 1 per cent.[76] This result would suggest either a tremendous excess under normal circumstances (also suggested by barium sulphate behavior) or great biologic activity. Traces of PTA, when infused, persist for a week as judged by effect on coagulation time[75] but the factor disappears in less than 24 hours when analyzed by prothrombin consumption tests.[75,76] Indeed, it has been observed in several instances now, that in vivo correction of the hemostatic defect by large amounts of plasma may be almost impossible to achieve. This fact is in sharp contrast to the expected beneficial effect of plasma which in vitro tests suggest.

PTA deficiency: This condition occurs as an inherited abnormality although isolated cases are known.[77] It affects males and females and is transmitted as a dominant with incomplete penetrance and no sex linkage. Therapy consists of the administration of ordinary banked plasma in amounts comparable to those used in hemophilia. The exact frequency with which plasma should be given has not been determined since prothrombin consumption correction is attained only briefly and when relatively large amounts of plasma are used.[78] Despite such failure of laboratory correction excessive bleeding has not been noted. Until the problem is further explored, a frequency of plasma administration similar to that employed in PTC and AHG deficiency should be followed.

Plasma thromboplastin factor D: This factor has been described by Spaet, Aggeler, and Kinsell[79] in a patient having laboratory features of thromboplastin deficiency but the defect could be corrected by AHG, PTC, and PTA deficient plasma. The factor is present in plasma and serum, is storage stable, and is not adsorbed by barium sulphate. Its true nature is under question.[80]

Hageman factor: This factor, distinct from other thromboplastin factors,[81] is present in plasma and serum; it is not adsorbed by barium sulphate and is heat stable. It is lacking in Hageman trait, an inherited disorder.[82] Despite laboratory evidence of defective coagulation, these patients do not have hemorrhagic episodes and therefore no need for therapy seems to exist. Transfusion of a small amount of stored plasma has been noted to correct the clotting time for 36 hours.[83]

Prothrombin Complex Deficiencies.—

Prothrombin: Prothrombin is now recognized as one of three factors essential for the formation of thrombin under the influence of thromboplastin and calcium. It is a glycoprotein found in Fraction III and is quite stable. It is found in normal plasma but is rapidly consumed in the clotting of normal blood so that only traces are found in serum. It is stable on storage and is readily adsorbed by barium sulphate. Prothrombin is presumably formed in the liver which requires vitamin K for an enzymatic step involved in its formation. Certain coumarin drugs, having a structural resemblance to vitamin K, inhibit prothrombin synthesis possibly by competitive interference.[84] It seems certain that naturally occurring K deficiency is identical with that induced by coumarin drugs.[85]

The critical level of prothrombin has been estimated to be 10 per cent[34,86] or less by the two-stage method of prothrombin determination. In pure prothrombin deficiency one-stage methods may give misleading results.[87] Fortunately, in almost all clinical conditions, prothrombin deficiency exists with stable factor deficiency[12,88] and the one-stage method is sensitive to such dual defects.[98] The survival time of prothrombin is about 36 to 72 hours.[6]

Labile factor (proaccelerin, plasma Ac-globulin, thromboplastin cofactor, factor V): Labile factor is a globulin found in Fractions II and III and in normal plasma; it is essential for thrombin formation. It is thermolabile and disappears from aging plasma, although much less so from citrated than from oxalated blood.[89] It is consumed during clotting and is found in trace amounts in serum normally.[90,91] Labile factor is not readily adsorbed by the adsorbants which remove prothrombin and stable factor. Vitamin K is not required[92] for its production nor is it influenced by coumarin drugs.[92,93] The critical level of labile factor is said to be 10 per cent[3] to 40 per cent,[12] with a survival time in the circulation of only 24 to 48 hours.[94]

Stable factor (proconvertin, serum prothrombin conversion accelerator, factor VII): As the name implies, this plasma factor is of unusual stability, and is found in Fraction III_2. It is essential for thrombin formation although its precise role is in considerable dispute. It is found in normal plasma, it is in more active form in serum, and during aging of blood increases in amount.[95] Agitation or thromboplastin supplementation of clotting blood increases the yield.[96] It is readily adsorbed by barium sulphate and requires Vitamin K for its production.[12] Dicumarol[97] and other coumarin drugs[98] reduce its concentration possibly faster and to a greater extent[85,99] than that of prothrombin. Its dependence on vitamin K implies a mode of formation closely related to that of prothrombin. The critical concentration is said to be from 4 per cent[100] to 40 per cent[101] with others estimating intermediate values of 10 per cent. The survival of stable factor in transfused patients is 24[102] to 36[19] hours.

Congenital deficiencies of the prothrombin complex factors: Isolated congenital deficiencies of each of the prothrombin complex factors are now known to exist. The reader is referred to the papers of Quick,[17,103] Owren,[12,94] Alexander,[102] and others[104-108] for descriptions of such cases. Many of the cases show a hereditary background. The therapy of these disorders is reserved for bleeding episodes in a fashion similar to that employed in hemophilia. Consideration of the characteristics of each factor, the critical level and known survival in the circulation, all indicated above, are guides to correct usage of blood or plasma in these conditions. Thus prothrombin and stable factor deficiency may be treated with banked blood or plasma while labile factor deficiency must be treated with freshly collected products. Amounts should be such as to contain a minimum of 300 ml. of plasma for adults and should be administered every 12 to 24 hours according to the clinical urgency. (It has been noted by Biggs and MacFarlane[5] that transfusions are surprisingly ineffective in correcting the abnormal coagulation tests associated with all the prothrombin complex deficiencies. However the failure to alter laboratory tests need not necessarily indicate a therapeutic failure. Stefanini[19] has wisely pointed out that the therapeutic effectiveness of administered plasma or serum may long outlast any trace of the administered factor as established by ordinary laboratory tests.)

"Hypoprothrombinemia" of liver disease: Deficiency of any or all factors may be found in liver disease.[88] Therapy consists of measures to improve liver function, replacement if severe hemorrhagic episodes* occur, preferably with fresh blood and the administration of vitamin K especially when associated with jaundice. The last measure will have no effect if liver damage is severe.

Vitamin K deficiency: Deficiencies of vitamin K from whatever cause are now known to be associated with a reduction in both prothrombin and stable

*Deficiencies of prothrombin complex factors are but a small part of the hemostatic defect of liver disease. Fibrinogen deficiency, fibrinolysis,[109] and vascular factors[110] are of importance and must be evaluated.

factor[12] to variable levels. Since naturally occurring vitamin K is fat soluble, deficiency is found in the presence of steatorrheas and biliary obstruction or fistulae. Various diarrheal states, and defective elaboration of vitamin K by intestinal bacteria, whether induced (antibiotic administration) or naturally occurring (neonatal), are other causes for deficiency. Neonatal hypoprothrombinemia, now considered to be a combined deficiency of prothrombin and stable factor[111-113] is the most probable cause of hemorrhagic disease of the newborn. The administration of vitamin K prophylactically to the mother prior to delivery[113] or to the child following delivery[112] will prevent the expected fall of these two factors although they do not restore levels to normal. This evidence would seem to indicate certainly that vitamin K deficiency is important in the pathogenesis of hemorrhagic disease of the newborn.

Finally, the administration of coumarin drugs may be considered to be an example of induced K deficiency.

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The therapeutic use of vitamin K has been complicated by a multitude of preparations. It is sufficient to be acquainted with the fact that the synthetic vitamins are water soluble (with the one exception of Menadione) and naturally occurring vitamins are fat soluble. The following principles for use of vitamin K should be observed.

1. All patients with hypoprothrombinemia whether associated with liver disease or not, or whether thought to be congenital or not, deserve a trial if feasible of a potent K preparation. If a water-soluble preparation does not appear effective, a potent fat-soluble preparation may be.[5] The superiority of naturally occurring fat-soluble preparations over synthetic water-soluble preparations is clearly demonstrated by experience with the hypoprothrombinemia associated with coumarin toxicity and in certain rare instances of "idiopathic" hypoprothrombinemia. As might be anticipated, hypoprothrombinemia due to severe liver disease or on a congenital basis responds to neither type of vitamin K preparation. The use of vitamin K is urged in all cases of hypoprothrombinemia, nevertheless, since the exact basis for the prothrombin deficiency may not be immediately known. Furthermore, the response to the administered vitamin K constitutes in itself a valuable clue as to the causation of the prothrombin lack.

2. Fat-soluble vitamin K cannot be adsorbed when administered orally in the presence of obstructive jaundice or biliary fistulae unless given with bile salts. In obstructive jaundice, such administration is undesirable. Fat-soluble vitamin K can be given intramuscularly in oil (Menadione 2 mg. injection) or a water-soluble vitamin may be used orally, intramuscularly, or intravenously.

3. The synthetic water-soluble vitamin K preparations are virtually without action in the therapy of hypoprothrombinemia associated with coumarin toxicity.[114-116] The fat-soluble K_1 emulsion preparation should be used intravenously if active bleeding is occurring, intravenously or orally if the problem is merely an excessively prolonged prothrombin time. In adequate dosage (50 mg. to 150 mg. of K_1 emulsion) the prothrombin time will be in a safe range in 3 hours.[115,117] The emulsion, which is supplied in a concentration of 50 mg. per c.c., should be diluted with sterile water for injection or isotonic saline so

that a final concentration of 10 mg. per c.c. is obtained. This should be administered intravenously at a rate not to exceed 1 c.c. per minute. Smaller doses may be used if anticoagulant therapy is to be continued and no acute hemorrhagic episode is present.

4. Even K_1 emulsion intravenously has a lag phase. In dangerous bleeding, the administration of K_1 emulsion should always be supplemented by transfusions which need not be fresh.

The miscellaneous conditions associated with labile factor deficiency listed in Table II are all treated with fresh blood transfusions. In an unusual case of labile factor deficiency associated with an antithrombin, exchange transfusion was used successfully.[118]

Fibrinogen Deficiencies.—

Fibrinogen: This protein, present in the plasma in a concentration of 250 to 400 mg. per 100 ml. has a molecular weight of 350,000. It is rich in glutamic and aspartic acids and contains some carbohydrate. Under the influence of thrombin, it is altered to fibrin through a complex process of polymerization.[119] It is stable on storage and is found in Fraction I. It has a survival following transfusion of about 4 days.[10] The critical level of fibrinogen has been indicated to be about 60 mg. per 100 ml. of plasma.[110,120] However, bleeding has been observed at levels of 100 mg. per 100 ml. and thus the latter value should be considered to be the critical level. A complex enzymatic mechanism for the destruction of fibrin and also fibrinogen is present in the blood and is activated under a variety of circumstances. Its characteristics have been admirably detailed by Astrup.[121] Fibrinogen (and fibrin) are also attacked by lysins of prostatic origin[122] and possibly other tissue fibrinolysins. The importance of fibrinolysis as a cause of fibrinogen deficiency may be gleaned from Table III in which the conditions indicated by an asterisk are associated with fibrinolysis of varying intensity.

Hereditary, congenital afibrinogenemia: This rare defect has been extensively studied.[23,123] It is treated with fibrinogen or blood during bleeding episodes which are infrequent.

The acquired afibrinogenemias are far more common and constitute acute medical emergencies.

Hypofibrinogenemia of liver disease: This condition, previously mentioned, is usually associated with multiple defects during far-advanced liver failure. Therapy is best handled by fresh whole blood.

Hypofibrinogenemia of pregnancy: Hypofibrinogenemia or afibrinogenemia associated with pregnancy is being more frequently recognized as a result of a greater awareness of this condition. The entire subject has been reviewed in a comprehensive article by Ratnoff, Pritchard, and Colopy.[124] Although the exact mechanism for the production of hypofibrinogenemia is not clear, the currently favored theory is one of intravascular defibrination as the result of placental thromboplastic infusion.[125,126] In cases associated with fibrinolysis it is thought that an additional mechanism for fibrinogen reduction has been superimposed. It is important to realize that afibrinogenemia or hypofibrinogenemia of pregnancy is somewhat of a misnomer since the depletion of coagulation factors may involve labile factor,[127] prothrombin,[127,128] antihemophilic globulin, and platelets[128] as well as fibrinogen (Tables I and II).

TABLE I. PLASMA THROMBOPLASTIN FACTOR DEFICIENCIES

I. Antihemophilic globulin deficiency
  (a) Hereditary, congenital lack—classical hemophilia, hemophilia A, etc.
  (b) "Sporadic" antihemophilic globulin deficiency
  (c) Vascular hemophilia (combined pseudohemophilia and AHG lack)
  (d) Circulating anticoagulants (anti-AHG)
    1. Hemophilia
    2. Post-partum
    3. "Symptomatic," collagen disorders
    4. Idiopathic
  (e) AHG lack associated with hypofibrinogenemia
II. Plasma thromboplastin component deficiency
  (a) Hereditary, congenital lack—Christmas disease, hemophilia B
  (b) Circulating anticoagulants
    1. Hemophilia B
    2. Others
  (c) Associated with vitamin K lack (anticoagulant therapy, neonatal)
III. Plasma thromboplastin antecedent deficiency
  (a) Hereditary, congenital
  (b) "Sporadic" (?)
IV. Fourth thromboplastin component deficiency
V. Hageman trait

TABLE II. PROTHROMBIN "COMPLEX" DEFICIENCIES

CONDITION	PROTHROMBIN DEFICIENCY	STABLE FACTOR DEFICIENCY	LABILE FACTOR DEFICIENCY
Congenital lack	+	+	+
Inherited lack	?	+	+
Liver disease	+	+	+
Vitamin K deficiency	+	+	−
Coumarin drugs	+	+	−
Postoperative states	+	?	+
Fibrinogenopenia, pregnancy	+	?	+
Terminal carcinoma	+	?	+
Purpura fulminans	−	−	+

+ Present.
− Absent.
? Unknown.

TABLE III. FIBRINOGEN DEFICIENCIES

I. Congenital afibrinogenemia or hypofibrinogenemia
II. Acquired:
  (a) Liver disease*
  (b) Afibrinogenemias of pregnancy
    1. Premature separation of placenta*
    2. Amniotic fluid embolism*
    3. Toxemia of pregnancy*
    4. Intrauterine retention of dead fetus*
    5. Idiopathic
  (c) Neoplasia
    1. Metastatic carcinoma of prostate*
    2. Carcinoma of pancreas*
    3. Carcinoma of stomach*
    4. Metastatic carcinoma of colon*
    5. Leukemia
  (d) Surgery
    1. Shock*
    2. Pulmonary manipulation*

*Reported in association with fibrinolysis as well.

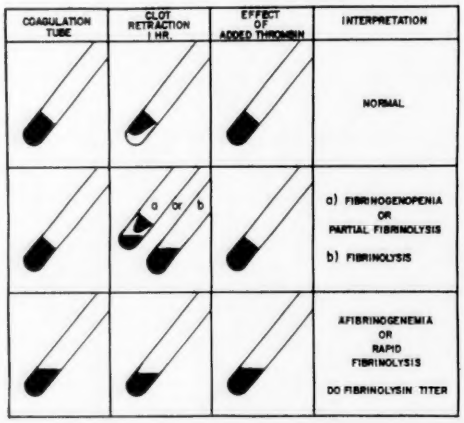

Fig. 4.—The detection of hypofibrinogenemia by means of simple clot observation with and without added thrombin.

Except for hypofibrinogenemia associated with a retained dead fetus, which may have a gradual onset,[124] the other events in pregnancy associated with this deficiency lead to an acute, precipitous change in the patient's status. Such a disaster calls for unhesitating coordinated effort on the part of all concerned. Early recognition of the development of hypofibrinogenemia is of importance and is facilitated by the removal of blood for clot observation (Fig. 4) upon

admission to the hospital if the patient is in labor, or twice weekly on an ambulatory basis if death of the fetus is suspected. Any unusual bleeding should call for immediate repetition of clot observation and, if time permits, fibrinogen determination by some of the newer rapid methods.[129-131] We have found that not infrequently time permits only the most rapid of laboratory observations upon which a decision must be made. The routine followed by Ratnoff and associates[124] should be consulted by all who have the responsibility for handling obstetrical cases.

While whole blood transfusion may provide enough fibrinogen in the mildest of cases, as indicated earlier, concentrated fibrinogen preparations, first used by Moloney, Egan, and Gorman[132] in this disorder and now fortunately in good supply both commercially and from Red Cross sources, must be used. Four grams are infused at once followed by additional amounts given according to the clinical condition and observations of the clot. Three to 8 Gm. are usually required although much larger amounts may be necessary if a fibrinolysin is present. Shock and blood loss should be combated with fresh blood to restore other depleted coagulation factors. Levophed infusion may be required in those cases in which intractable shock appears (in our experience, a symptom indicative of amniotic fluid embolism). Fluid balance and renal function must be carefully followed. Attempts to deliver the fetus whether from above or below should not be undertaken until hemorrhage appears under adequate control. Although the restoration of fibrinogen levels may occur promptly on termination of the delivery, it may take several days for full restoration if shock has been protracted. The recovery may also be complicated by thrombocytopenia which may last as long as 5 days. Although the thrombocytopenia is possibly related to the same mechanism as that which produces the hypofibrinogenemia, the use of large amounts of banked blood may be a factor in its production.[133] Scott[134] warns against the use of artificial macromolecular substitutes for blood (dextrans) in large amounts in afibrinogenemia because of the tendency for these compounds either to form complexes with fibrinogen or to facilitate deposition of fibrin. Triple or quadruple strength reconstituted plasma has been suggested as an adequate source of fibrinogen if pure fibrinogen is not available.[135]

Fibrinogen deficiency associated with a variety of malignant conditions and usually accompanied by fibrinolysis has been reported. Among these are carcinoma of the prostate,[136,137] pancreas,[138] stomach,[139] and colon,[140,141] and leukemia (Table III). Therapy consists of fibrinogen and blood replacement as indicated above. Attempts at treating the underlying condition are almost exclusively restricted to estrogen therapy of metastatic disease of the prostate with reduction and elimination of the circulating fibrinolysin. Stefanini and Gendel[142] have successfully used ACTH or cortisone in the control of fibrinolysis associated with this disorder, the suggested rationale being stimulation of antifibrinolysin activity or suppression of the fibrinolysin precursor.[6]

Other therapeutic agents: A multiplicity of systemic agents exists for which various clot-promoting activities have been claimed. Such preparations consist of dicarboxylic acids, snake venoms, vasoconstrictors, hormones, vitamins, etc. Some are harmless; others are not so harmless. Their use as a "broad spectrum"

substitute for an inquiry into the cause of bleeding is unjustified in an era in which the laboratory diagnosis of coagulation disorders is so advanced. Admittedly such a search is time-consuming and time may be a vital factor to a bleeding patient. It requires trained personnel and laboratory reagents not always available. But the reward of finding a specific coagulation deficiency is worth the effort. If a "shotgun" preparation must be used in an undiagnosed bleeding patient there is none better and more physiologic than fresh blood or plasma.

There do exist patients who bleed pathologically and for whom no ascribable coagulation defect can be uncovered however meticulous and arduous the search. As new techniques are evolved, this number may be expected to decrease. Until then, they will continue to tax the ingenuity of the clinician in management and stimulate the laboratory worker for improved diagnostic tests. In these patients any therapy which will do no harm is justified.

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THE RELATIVE FREQUENCY OF THE SEVERAL TYPES OF CHRONIC LEUKEMIA AND THEIR MANAGEMENT

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DEFINITION OF CHRONIC LEUKEMIA

CHRONIC leukemias have been defined as "those leukemias with an expected duration of life of one to twenty years or more, average three to five years . . . from the onset of the first symptoms. . . . The most differentiated stage of the involved series is always present, in addition to the less differentiated cells."[1] Because of the increasing frequency of therapeutically induced remissions in acute leukemia, the distinction of the chronic forms on a temporal and prognostic basis has less significance than formerly. Nevertheless, in spite of overlapping of survival times, the great majority of patients with chronic leukemia live much longer than those patients with the acute forms of the disease who experience most nearly complete remissions.

CLASSIFICATION

Proliferation of cells of the granulocytic or lymphocytic series characterizes most cases of chronic leukemia, and, in addition to their numerical importance, these forms merit preferential consideration because, as a rule, they may be well controlled by specific treatment. However, in the category of chronic leukemia there must also be placed some variants of myeloid and reticuloendothelial disease which are difficult to classify and are usually characterized by anemia and leukopenia, as well as by the presence of small numbers of atypical and poorly differentiated cells in peripheral blood and bone marrow. These processes frequently terminate in acute phases with rising leukocyte counts consisting of highly anaplastic cells. Such terms as "preleukemic myelopathy," "aleukemic myelosis," "malignant reticulosis," and "aleukemic monocytic leukemia" have been applied to this group of conditions.

It is sometimes difficult to delineate precisely the differences between leukemia and instances of chronic "nonleukemic" myeloproliferative disease, including some cases of polycythemia vera and agnogenic myeloid metaplasia. However, there should be little room for disagreement in classifying the great majority of cases of chronic leukemia and it is this group with which we are primarily concerned.

ETIOLOGIC CONSIDERATIONS

Since it is not possible to discuss measures designed to prevent or cure the leukemic disorders, the attention of epidemiologists and clinicians is necessarily restricted to consideration of factors which may have a bearing on the etiology or at least the occurrence of these conditions, and to evaluation and comparison of therapeutic agents and treatment regimens.

The relationships of geographical location, race, sex, and age to the incidence of the various types of leukemia and the relative frequencies of these types have little direct bearing on the etiology of the leukemias unless there can be shown a trend in incidence or a changing pattern of cytologic and clinical characteristics. If such changes can be convincingly documented it becomes significant to search for environmental factors which might appropriately be correlated with the occurrence of leukemias of specific types and with a relative propensity to affect particular segments of the population. Unfortunately, no meaningful correlations have so far been described, except that between exposure to ionizing radiation and the subsequent development of leukemia.[2-4]

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INCIDENCE AND RELATIVE FREQUENCY

Mortality statistics reveal a progressive rise in the incidence of leukemia since 1900.[5] This increase cannot be accounted for, in the main, by an aging population nor by improved diagnostic facilities. Because available mortality statistics obtained in successive years on large unselected populations give no information on cell types or classification on basis of acuity or chronicity, it has generally been necessary to obtain such data from restricted groups and in particular from hospital case series. The latter, in spite of a high degree of selection, have the advantage, if carefully studied, of uniform criteria of diagnosis and classification.

In 1942 and 1943, the author reported a series of cases of leukemia seen at the Simpson Memorial Institute of the University of Michigan from mid-1927 through the end of 1941, a period of 14½ years.[6,7] It may be of interest to compare some of the data for that period with the equivalent information for cases of leukemia observed during the period of 1942 to 1956 inclusive. Comparisons of sex, age, and type of leukemia should not be affected materially by influences tending to promote selection provided certain precautions are taken. Because of lack of uniform coverage of childhood cases of leukemia, all children under 14 years of age have been excluded from the study and the earlier series has been re-evaluated with omission of children. The diagnostic complexity of the earlier reports has been simplified so that only broad categories are considered, thus eliminating, it is believed, the danger of establishing differences which are merely the result of changes in diagnostic criteria. This also makes comparisons with other reports more feasible. The classifications employed are: (1) chronic granulocytic leukemia, which includes cases formerly listed as chronic myelocytic and chronic myelomonocytic; (2) chronic lymphocytic leukemia, which comprises cases formerly reported as chronic lymphogenous and chronic lymphosarcoma cell; (3) chronic monocytic leukemia, which was designated as chronic histiomonocytic in the earlier report and includes both

leukemic and subleukemic forms of malignant reticuloendotheliosis; (4) acute leukemia, which comprises all cases which come within the definitions of acute or subacute leukemias, as recommended by the Committee for Clarification of the Nomenclature of Cells and Diseases of the Blood and Blood-forming Organs.[1]

The incidence in the two time periods of the several types of leukemia and the sex distributions and median ages for the chronic forms of leukemia are shown in Tables I and II.

TABLE I. THE NUMBER OF CASES AND THE RELATIVE FREQUENCY OF THE CHRONIC FORMS OF LEUKEMIA AND OF ACUTE LEUKEMIA IN TWO CONSECUTIVE 15-YEAR PERIODS

PERIOD	CHRONIC LYMPHOCYTIC		CHRONIC GRANULOCYTIC		CHRONIC MONOCYTIC		ACUTE—ALL TYPES		TOTAL
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER
(1) 1927–1941	131	30.7	150	35.1	16	3.7	130	30.4	427
(2) 1942–1956	187	24.5	224	29.4	26	3.4	325	42.6	762
Per cent increase of period (2) over period (1)	69		72		78		125		

TABLE II. THE SEX DISTRIBUTION AND MEDIAN AGES FOR THE CHRONIC FORMS OF LEUKEMIA IN TWO CONSECUTIVE 15-YEAR PERIODS

TYPE OF CHRONIC LEUKEMIA	NUMBER OF CASES			PER CENT OF TOTAL CASES			PER CENT MALES			MEDIAN AGE		
	1927-1941	1942-1956	COMBINED	1927-1941	1942-1956	COMBINED	1927-1941	1942-1956	COMBINED	1927-1941	1942-1956	COMBINED
Lymphocytic	131	187	318	44.1	42.8	43.3	62.4	66.6	64.8	63	64	64
Granulocytic	150	224	374	50.5	51.3	51.0	52.9	52.7	52.7	46	44	45
Monocytic	16	26	42	5.4	5.9	5.7	87.5	80.8	83.3	45	48	47

From the data presented, two general conclusions, one of a positive and the other of a negative nature, seem warranted. First, the occurrence of acute leukemia in adults in proportion to the number of cases of chronic leukemia of all types appears definitely to be on the increase. During the period 1927 to 1941 the ratio of adult cases of acute leukemia to those of chronic leukemia was 0.44, whereas for 1942 to 1956 it was 0.77 in spite of a substantial increase in the number of cases of chronic leukemia. A further chronologic breakdown, which will be reported elsewhere, provides additional strong support for the growing incidence of acute as contrasted with chronic leukemia, since there is revealed a sustained trend with a present ratio of acute to chronic leukemia of about 1.0.

The second conclusion to be drawn from the case records of the two periods is that no evidence is afforded of a significant change in the sex or age incidence of chronic leukemia or of an alteration in the relative frequencies of the three types of chronic leukemia under consideration. No inference concerning overall increase in chronic leukemia is justified since, although in terms of total hospital registrations the number of cases of chronic leukemia has increased, it is not possible to weigh accurately factors which affect the referral of patients with a particular disease to a medical center.

These findings, therefore, do not support the suggestion of a shift in the sex ratio in recent years toward a higher proportion of females with chronic granulocytic leukemia[8] nor of a change in relative frequency of chronic lymphocytic and chronic granulocytic leukemia favoring the former.[9]

THERAPEUTIC CONSIDERATIONS, THE DECISION TO INSTITUTE OR WITHHOLD TREATMENT

A much greater variety of clinical manifestations and a broader range of hematologic changes characterize chronic lymphocytic leukemia than is true of the granulocytic type. It is this lack of homogeneity of the lymphocytic form of the disease that provides grounds for prognostic differentiation and criteria for the selection of antileukemia therapy or deferral of specific treatment.

When a new case of chronic granulocytic leukemia is under consideration there is usually little to indicate whether the disease is likely to run its course in one year or three or six. The choice of treatment will depend on the interest of the physician, or on extraneous factors such as availability of a particular medication or ease of follow-up examinations, except that in an occasional patient severity of pressure manifestations from a greatly enlarged spleen may determine the decision to employ x-radiation over the splenic region. In the patient whose granulocytic disease is discovered as an incident of medical evaluation for an unrelated condition or during a health examination, specific therapy may be postponed until symptoms develop. There is no evidence that later control of the disease or length of survival is adversely affected by such deferment. However, in almost every instance, the disease progresses during the interval of no therapy, and omission of treatment is rarely feasible for longer than a few months. It is largely for this reason that many clinicians, including the writer, institute specific therapy for chronic granulocytic leukemia as soon as the diagnosis is made. The advantages of so doing are partly psychological, with strengthening of the physician-patient relationship, greater assurance of cooperation, and avoidance of the disheartening and sometimes confidence-losing effect which many patients experience when they are told after a short period of observation that their disease has entered a new phase requiring treatment with radiation or drugs.

The situation with respect to therapy for chronic lymphocytic leukemia is quite different. Here there may be no signs of progress of the disease for many months or even years. Since the success of all specific treatment of leukemia depends upon the establishment of a patient-disease (? host-tumor) relationship favoring the former, there seems to be no justification for interfering when such a favorable relationship already exists.

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When confronted with a case of chronic lymphocytic leukemia in which the patient is without symptoms attributable to the disease, anemia or thrombocytopenia are not present, and the leukocyte count, although elevated, is not progressively rising, it is the writer's practice to advise the patient that a period of observation is desirable before deciding on a management regimen. This waiting period, with re-evaluation at intervals at first of 2 months, later as long as 6 months, may be prolonged indefinitely. An illustration is provided by a man, now aged 63 years, who has been observed by the writer for 12 years. The diagnosis of chronic lymphocytic leukemia was made in 1945, no treatment has ever been given, and there are no signs of progress of the disease. There are small, soft lymph nodes in cervical and axillary regions, and for the past 5 years the spleen has been felt 2 to 3 cm. below the costal margin. The total leukocyte count is usually between 15,000 and 20,000 per cubic millimeter and the lymphocytes, mostly small and well differentiated, range between 60 per cent and 80 per cent. It may be objected that this is not a case of leukemia but some form of benign lymphocytosis. Perhaps so, but there appears to be no way of making such a distinction, except in retrospect, nor can this patient be assured that his disease will never enter a phase requiring antileukemia therapy.

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OBJECTIVES OF THERAPY

The two major objectives of specific as opposed to supportive therapy in chronic leukemia are (1) attack on the systemic disease, with elimination or at least diminution of such manifestations as anemia, tendency to hemorrhage, thrombosis and infarction, unusual susceptibility to infection, fever, and weight loss; and (2) relief of effects caused by local tumefaction exerting pressure, compression, and obstruction, or by particular organ or tissue infiltration producing functional changes.

Therapy directed toward particular lesions is essentially limited to locally applied radiation with surgical procedures occasionally indicated. In this connection, resection of the spleen in leukemia is rarely justifiable even in the presence of secondary "hypersplenic" hemolytic anemia or thrombocytopenia, since such manifestations can usually be well controlled with moderate sized doses of the corticosteroids. However, some patients with chronic lymphocytic leukemia require increasing amounts of these hormones, exceeding limits of tolerance, and in such situations splenectomy may be of great benefit. In granulocytic leukemia removal of the spleen is characteristically followed by rapid enlargement of the liver and refractoriness to all available forms of therapy.

Measures available for systemic treatment of chronic leukemia will receive individual consideration and will be discussed in relation to the various types of the disease.

CHEMOTHERAPY IN CHRONIC LEUKEMIAS

Although drug therapy of leukemia, namely with inorganic arsenic as Fowler's solution, or with benzol, has a long history, the management of patients with chronic leukemia was for many decades almost exclusively within the province of the radiologist.

The introduction of a number of new chemical agents for the treatment of leukemia and lymphoma during the past decade has provided the clinician with a choice of therapeutic methods and has placed upon him a corresponding degree of responsibility not only for wise selection but, of even greater importance, for familiarity with the general properties and potentialities of the drugs he uses, and for careful individualized follow-up evaluation of his patients.

Interest in the novel is understandable and every new type of agent capable of affecting the course of leukemia should receive critical evaluation. But for a drug to compete successfully for a place in the therapy of leukemia it should be at least as effective in terms of adequacy of control and mean survival as existing methods of treatment, or it should possess unique properties which render it preferable in special situations.

Of the drugs found to be effective in chronic leukemias, arsenic and benzol are not of contemporary interest. There remain for consideration urethan, deacetylmethyl-colchine (Colcemide, Demecolcin), the antimetabolites (essentially limited to 6 mercaptopurine, Purinethol and its analogues), and certain polyfunctional alkylating agents.

Much effort is currently being spent by cooperating clinical groups throughout the United States on the comparative evaluation of chemical agents in the treatment of leukemia and other forms of disseminated neoplastic disease. The rigidity of the criteria for case selection, follow-up, and measurement of response, and the statistical analyses required, should yield much useful information, especially in the matter of dosage schedules and the possible merits of combination and sequential therapy. Furthermore, the experience gained from the preparation and application of protocols and the pooling of observations by a number of cooperating clinical investigators will undoubtedly prove immensely valuable in the evaluation of new agents. However, sufficient experience, even though not carefully controlled, has already been gained to render it unlikely that the conclusions to be drawn from the statistically superior data collected by the cooperating groups will result in any general or major change in the currently held views on therapeutic agents which are presently available.

RADIATION THERAPY

The standard of reference for chemotherapy of chronic leukemia is ionizing radiation, yet radiation has been employed in a variety of ways, such as regional x-ray therapy (usually to spleen or enlarged lymph nodes) or total body exposure, intensive dosage short courses or prolonged periods of low dose administration. Radiation has been by x-ray and by internal radioisotope therapy, usually administered as radioactive phosphorus (P^{32}). According to Tivey,[10] who analyzed survival figures for a large number of patients with granulocytic or lymphocytic leukemia reported in the literature through 1951, there is no difference between the survival prospects in the two forms of leukemia, and half the patients in any series comparably treated may be expected to survive for 2.65 years after the development of symptoms or 1.6 years after commencement of therapy. Tivey applied the same analytical techniques to a series of cases of chronic granulocytic and lymphocytic leukemia treated by Osgood with regularly spaced P^{32} or total

body roentgen irradiation in doses designed to maintain the leukocyte count between 10,000 and 20,000 per cubic millimeter.[11] He concluded that in this series a survival of half the patients for 4.8 years from the onset of symptoms could be predicted. Of course, other factors than specific therapeutic methodology enter into comparisons of this sort, especially the extent to which the principle of total patient care is applied and the recent advances in blood transfusion therapy, control of intercurrent infections, and management of hemorrhage and secondary hemolytic disease. Nevertheless, it is the writer's opinion that continued even control of the leukemic process as long as possible not only promotes a sense of well-being in patients so treated but also results in increased survival times.

CHRONIC GRANULOCYTIC LEUKEMIA

Since 1940, the following agents other than x-radiation have been used at the Simpson Memorial Institute in the therapy of chronic granulocytic leukemia: radioactive phosphorus, 87 cases; urethan, 36 cases; triethylene melamine (TEM), 41 cases; 1-4, dimethanesulfonyloxybutane (Myleran), 31 cases; and deacetylmethylcolchicine (Colcemide), 7 cases. In addition, a few patients have received in clinical trials drugs no longer used for this purpose, and a number of patients with advanced granulocytic leukemia not responsive to the agents listed above have received 6-mercaptopurine (Purinethol), or another antipurine.

For systemic therapy in chronic granulocytic leukemia, total body x-radiation and radioactive phosphorus (P^{32}) have been almost completely replaced in recent years in our institution by the two chemically unrelated alkylating agents, Myleran and TEM.

Irradiation, usually in the form of P^{32}, is employed when frequent follow-up examinations and blood counts (as a rule every 2 to 4 weeks) are not feasible. The usual initial dose of P^{32} is from 4 to 8 mc. administered intravenously depending on the size of the patient and the evidences of activity of the disease. The patient is seen in 6 to 9 weeks when a second dose of 2 to 4 mc. intravenously may be given if satisfactory control has not been obtained. Subsequent return visits may be extended to 3- to 6-month intervals. It must be stated, however, that in the writer's view interval therapy of chronic granulocytic leukemia based on recurrence of signs of activity does not provide as satisfactory control as the regularly spaced administration of radiation as advocated by Osgood,[11] or the continued use of a chemotherapeutic agent.

It is recognized that an occasional patient with chronic granulocytic leukemia will enter prolonged remission after a single course of x-ray therapy, one dose of radioactive phosphorus, or a period of drug administration. An example of such responses is provided by a woman first seen by the writer in May, 1952, at the age of 39 years. She complained of fatigability, nervousness, and discomfort in the left upper quadrant of 8 months' duration. The spleen descended 7 cm. below the left costal margin and the liver was moderately enlarged. The leukocyte count was 76,000 per cubic millimeter with a differential count characteristic of chronic granulocytic leukemia. The hemoglobin value was 11.5 Gm. per 100 c.c. and the platelet count was elevated. Sternal marrow aspiration

provided a highly cellular specimen with granulocytic hyperplasia and striking increase in progranulocytes and myelocytes. The M:E ratio was 10:1 and megakaryocytes were extremely numerous. After 2½ months of observation without treatment, the leukocyte count had increased to 99,000 with myeloblasts 4 per cent, progranulocytes 4 per cent, myelocytes 7 per cent, metamyelocytes 21 per cent, band neutrophils 18 per cent, segmented forms 38 per cent, eosinophils 1 per cent, lymphocytes 5 per cent, and monocytes 2 per cent. Radioactive phosphorus was administered intravenously in a single dose of 7.6 mc. Remission occurred promptly and has continued without any form of treatment up to the time of reporting. When last seen in March, 1957, nearly 5 years after her first visit, she was asymptomatic and the spleen tip was felt just at the costal margin on deep inspiration. The leukocyte count was 6,150 and the hemoglobin value 13.2 Gm. A few immature granulocytes were observed on the stained blood film, but the most striking abnormality was a basophil count of 21 per cent. Platelets were very numerous. Remissions such as this in chronic granulocytic leukemia, although rarely of such long duration, are sufficiently frequent to render it hazardous to base comparisons of intermittent versus continued therapy on small numbers of cases treated by either method.

Urethan (ethyl carbamate) was shown by Paterson and her associates,[12] in 1946, to have effects in chronic leukemia comparable to those obtained with x-ray therapy. Urethan found a place in the treatment of chronic granulocytic leukemia because of its ease of administration and relative freedom from production of rapid severe bone marrow depression. Thrombocytopenia is not produced, but in patients receiving prolonged medication with urethan, profound leukopenia sometimes develops.

Urethan reached the peak of its popularity at the Simpson Memorial Institute in 1947, 1948, and 1949. During those years 29 cases of chronic granulocytic leukemia received initial therapy with urethan. Of the total of 36 cases, 6 of whom had been treated previously with radiation and one with Fowler's solution, 13, or 36 per cent, obtained remissions which were classified as "excellent" or "good," as defined later; 17, or 47 per cent, had only fair responses; and 6, or 17 per cent, received little or no benefit from urethan even though the status of their disease was not far advanced when treatment was begun. Conceding that the small size of this series precludes generalizations concerning the effectiveness of urethan, it is nevertheless probably significant that in only 13 of 36 cases, none of them far advanced when treated, was there reasonably good control of the disease for 4 months or longer.

Even before newer drugs became available, enthusiasm for the use of urethan in chronic granulocytic leukemia was on the wane since it became increasingly evident that control was not as readily maintained with this drug as with ionizing radiation.

The most promising compounds so far used in the treatment of chronic leukemia and lymphoma are those possessing alkyl groups which are capable of reacting chemically with constituents of the nuclei of proliferating cells and so exerting cytotoxic effects, especially on growing cells of the hemic and lymphatic systems and the epithelial cells of the alimentary tract. These alkylating

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agents exist in a wide variety of chemical structures of which two classes, the nitrogen mustards and the sulfonic acid esters, have found most extensive application in medicine.

"Nitrogen mustard" (methyl-*bis* (β-chloroethyl) amine hydrochloride, HN2, Mustargen) was the first alkylating agent to be introduced into cancer chemotherapy.[13] This drug, even in the early days of its use, did not receive wide acceptance in the treatment of chronic leukemia, for reasons which are not entirely clear, but which probably have to do in part with the recommended dosage. The usual dose of HN2 per course of treatment is stated to be 0.4 mg. per kilo given intravenously generally in four divided amounts on consecutive or alternate days followed by an interval before the next treatment of at least 6 weeks. This amount, ranging between 20 and 30 mg. for most adults, is, in general, much too small for patients with chronic granulocytic leukemia and too large for many of those with chronic lymphocytic leukemia. There is no reason to conclude that HN2 would not prove to be as valuable as TEM, which we have shown to be as effective as Myleran in the treatment of chronic granulocytic leukemia, provided that a judicious plan of administration were employed which would yield adequate treatment to achieve the desired result without serious risk of overdosage. HN2 does, however, possess the drawbacks of requiring especially careful intravenous administration and of producing acute nausea and vomiting. The latter effects can largely be obviated by the prior administration of 25 or 50 mg. chlorpromazine, followed by a second dose 3 hours after HN2 administration.

Demonstration of the human antitumor activity of triethylene melamine (TEM), in 1950, by Rhoads and others[14] was followed by extensive application of this drug to the treatment of leukemia and lymphoma. From these clinical trials there emerged the general impression that, in respect to leukemia, TEM was of greatest usefulness in the chronic lymphocytic form of the disease, in spite of adequate documentation of its effectiveness in chronic granulocytic leukemia.[15] The similarity in chemical structure between HN2 and TEM, as polyfunctional alkylating agents, undoubtedly was instrumental in suggesting the major indications for use and the mode of therapy of the latter drug; namely, emphasis on the lymphoid rather than myeloid neoplasms, and the preference for intermittent courses of administration rather than continued therapy.

Therefore, when Myleran was reported to be effective in chronic granulocytic leukemia,[16] its different chemical structure from the mustards seemed to explain the supposed preferential action of Myleran on myeloid and of HN2 and TEM on lymphoid proliferative disease. On the contrary, the only demonstrable differences in biologic action between the two classes of alkylating agents are of a quantitative rather than qualitative nature and have to do with rates of absorption, diffusion into cells, and chemical reactivity.[17]

At the Simpson Memorial Institute 41 patients with chronic granulocytic leukemia were treated with TEM during the years 1951 to 1956, and 31 patients were treated with Myleran between 1953 and 1956. Some of these patients had received other medication, such as radiation, urethan, or Colcemide prior to being placed on TEM or Myleran. Some were in a relatively early well-dif-

ferentiated stage of their disease whereas in others the disorder was advanced and many of the granulocytes in the peripheral blood were immature. In this category are placed cases of far-advanced disease, with predominance of myeloblasts and atypical progranulocytes in blood and marrow, as well as cases of moderately advanced disease, since the distinction between such degrees of severity is arbitrary and often will vary among different clinicians. On the other hand, there is rarely disagreement over classifying a case in the early well-differentiated stage. The patients were classified in terms of the quality and duration of their therapeutic responses according to the following criteria. Excellent: leukocyte count less than 15,000 per cubic millimeter with early granulocytes (myeloblasts through metamyelocytes) below 5 per cent; normal hemoglobin and volume of packed red cells; free of symptoms referable to leukemia; spleen not palpable or barely palpable; duration in this status 6 months or longer. Good: leukocyte count less than 50,000 with early granulocytes below 20 per cent; hemoglobin above 11 Gm. or volume of packed red cells above 30 per cent; virtually asymptomatic; splenomegaly less than before treatment; duration in this status or better 4 months or longer. Fair: leukocyte count and early granulocyte percentage reduced below pretreatment levels; hemoglobin and volume of packed red cells essentially stable; no serious incapacitation; duration in this status or better 2 months or longer. Poor: disease not under hematologic or clinical control; serious incapacitation; duration in this status indeterminate.

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TABLE III. CHRONIC GRANULOCYTIC LEUKEMIA TREATED WITH TRIETHYLENE MELAMINE

THERAPY	NUMBER OF CASES	DOSAGES	THERAPEUTIC RESPONSES AND STATUS OF DISEASE†			
			EXCELLENT	GOOD	FAIR	POOR
Untreated before TEM intermittent courses	7	5 mg. each of 2-10 doses	0	3 (All early)	2 (Both advanced)	2 (Both advanced)
Untreated before TEM continuous administration	2	5 mg. monthly to 5 mg. weekly	1 (Early)	1 (Advanced)	0	0
Other treatment before TEM intermittent courses	32	5 mg. each of 2-13 doses	0	9 (3 early) (6 advanced)	6 (2 early) (4 advanced)	17 (All advanced)
Other treatment before TEM continuous administration	4*	5 mg. monthly to 5 mg. weekly	1 (Early)	2 (1 early) (1 advanced)	0	1 (Advanced)
Total	41		2	15	8	20

*Included in cases receiving prior intermittent treatment.

†These categories include 4 duplications, resulting from some patients receiving both intermittent and continuous therapy.

Summaries of our therapeutic experience with triethylene melamine and Myleran are presented in Tables III and IV. The TEM and Myleran groups are not strictly comparable because the agents became available at different times and there was a tendency to employ TEM, in the early period of its use, in cases which were becoming difficult to control with radiation or urethan, whereas Myleran was introduced as an effective form of therapy for chronic granulocytic leukemia and was used from the outset as initial treatment for many patients with this disease. Thus of the 41 cases of chronic granulocytic leukemia treated with TEM 10 are classified as early and 31 as advanced, 9 had had no previous treatment, and 32 had received earlier therapy, whereas of the 31 cases treated with Myleran 16 are described as early and 15 as advanced, 12 had had no prior antileukemia medication, and 19 had been previously treated. These differences between the two groups of patients, coupled with the fact that some time elapsed after TEM was introduced before the importance of continuous therapy was appreciated, are probably sufficient to explain the apparently superior results obtained with Myleran as shown by 8 excellent and 18 good responses in contradistinction to the 2 excellent and 15 good responses obtained with TEM.

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TABLE IV. CHRONIC GRANULOCYTIC LEUKEMIA TREATED WITH MYLERAN

THERAPY	NUMBER OF CASES	DOSAGES	THERAPEUTIC RESPONSES AND STATUS OF DISEASE*			
			EXCELLENT	GOOD	FAIR	POOR
Untreated before Myleran intermittent courses	6	12 – 6 – 4 mg. 10 – 15 – 30 days	0	5 (All early)	0	1 (Early)
Untreated before Myleran continuous administration	6 (+ 4*)	2 mg. 3 × weekly to 2 mg. daily	6 (All early)	1 (Advanced)	2 (Both advanced)	1 (Advanced)
Other treatment before Myleran intermittent courses	9	12 – 6 – 4 mg. 10 – 15 – 30 days	0	3 (2 early) (Advanced)	1 (Early)	5 (1 early) (4 advanced)
Other treatment before Myleran continuous administration	10 (+ 6*)	2 mg. alt. days to 2 mg. daily	2 (Both early)	9 (6 early) (3 advanced)	1 (Early)	4 (1 early) (3 advanced)
Total	31		8	18	4	11

Underlined values are usual doses and time periods.
*Prior intermittent treatment.
†These categories include 10 duplications, resulting from some patients receiving both intermittent and continuous therapy.

The collective recorded experience of many clinics supports the conclusion that Myleran is an effective and exceedingly useful agent for the treatment of chronic granulocytic leukemia. The longest experience is that of the Chester

Beatty Research Institute as reported by Galton.[18] He has presented data on 42 cases of chronic granulocytic leukemia treated with Myleran and on 3 in which the analogue dimethyl-Myleran was used. Small initial doses (65 mcg. per kilogram) were found to be as effective as larger amounts in inducing symptomatic relief and increase in hemoglobin, but the larger doses were followed by more rapid decline in the leukocyte count and regression in spleen size. Continuous therapy was used in 25 cases and was found to be especially useful when the leukocyte count rose rapidly after completion of a course of therapy. Maintenance doses ranged between 0.5 and 2.0 mg. daily. It has been found that maintenance dosage must be increased with the passage of time, usually as increments of 0.5 mg. per day every 6 to 8 months.

In common with other observers Galton found bone marrow aplasia to be the only serious toxic effect of Myleran. Such an event was observed twice in his series. One patient received unusually large doses and the other continued taking small doses without supervision. Other side effects in patients receiving Myleran include amenorrhea, minor degrees of pigmentation of the skin, and occasionally gynecomastia.

Galton reported that 34 of his patients were dead and the median survival from the *time of diagnosis* was 36 months compared with 26 months in a group of 33 patients treated with radiotherapy alone before 1950. Assuming that the time of diagnosis was also the time when therapy was begun, a survival of 50 per cent of patients with chronic granulocytic leukemia for 3 years compares favorably with the longest survival figures previously reported, namely, those of Osgood and Seaman[19] as analyzed by Tivey.[10] However, it should not be inferred that the evidence as yet is conclusive that Myleran is superior to x-radiation or radioactive phosphorus in the treatment of chronic granulocytic leukemia. It does appear warranted to regard Myleran as at least equal to radiation in therapeutic effectiveness and as having other advantages, including ease of administration and dosage control, which render it the preferred form of therapy for the majority of patients with this disease.

Colcemide or Demecolcin, like colchicine, owes its cytostatic properties to mitotic inhibition with blocking at the metaphase. However, Colcemide is some 30 times less toxic, with respect to gastrointestinal manifestations, than colchicine, and consequently may be given in relatively large doses and for long periods of time. Colcemide was first used in the treatment of chronic granulocytic leukemia by Moeschlin and his associates,[20] and Moeschlin later reported observations on 30 patients extending over a period of 3½ years with generally favorable results.[21] An initial dosage of 4 mg. of Colcemide daily, divided into two doses given orally morning and evening, is recommended. A few patients required doses as high as 10 mg. daily. As soon as the leukocyte count has fallen to a level of 30,000 per cubic millimeter, Moeschlin recommends that the medication be discontinued for 3 or 4 days and then resumed in maintenance dosage, which is usually about one-third of the initial level, but must be adjusted to individual requirements.

Our limited experience with Colcemide in the treatment of chronic granulocytic leukemia has led us to the conclusion that the effects of this drug are less

dependable than those of Myleran or TEM, that the dosage is harder to regulate, and that unpleasant, but not serious side effects, are more common. These include digestive symptoms and alopecia. The major and perhaps the only indication for Colcemide in the treatment of leukemia is, as Moeschlin emphasizes, in the proliferative and poorly differentiated phase which many patients with chronic granulocytic leukemia enter during the terminal period of their illness. Moeschlin has reported favorable responses in 3 of 5 patients with terminal myeloblastic transformation. The experience of others in this connection has been varied, but on the basis of the small number of cases reported it appears justifiable to conclude that, although any great benefit is unlikely, Colcemide is worthy of a trial when radiation and the alkylating agents, Myleran and TEM, no longer effectively control proliferation of cells in chronic granulocytic leukemia.

There remains to be considered the place of metabolic antagonists in the treatment of chronic granulocytic leukemia. The 4-amino analogues of pteroylglutamic acid or "anti-folics" (methotrexate and Aminopterin) were found to produce temporary improvement in most cases of early granulocytic leukemia[22] but the development of severe toxic manifestations during the course of treatment precludes their use in this condition. Patients with advanced granulocytic leukemia have only rarely been even temporarily benefited by compounds of this class. The place of the antipurine, 6-mercaptopurine (Purinethol), is somewhat more favorable. The collective experience of a number of clinical investigators[23] attests to the efficacy of this drug in most cases of early chronic granulocytic leukemia. However, the disorder is not as well controlled with this agent as with Myleran or TEM and relapse almost invariably occurs as soon as the medication is discontinued. There is a place, however, for Purinethol administered by mouth in a daily dose of 2 to 3 mg. per kilo in the advanced stage of granulocytic leukemia when it may effectively suppress for a time leukemic cell proliferation even though the disease has become unresponsive to radiation and the alkylating antileukemia agents.

CHRONIC LYMPHOCYTIC LEUKEMIA

The great variability in the clinical course and response to treatment, as well as the indications for therapy in chronic lymphocytic leukemia, make it unrealistic to attempt to establish the preferred therapeutic regimen for this condition. Furthermore, comparisons of therapeutic results obtained in different case series, while always subject to bias in leukemia, are especially so in respect to the chronic lymphocytic form of the disease. The clinician who treats every case of chronic lymphocytic leukemia when first seen with a particular form of radiation or a new polyfunctional alkylating agent will report much better results than his colleague who withholds therapy in cases that do not appear to be progressive.

Although the indications for therapy are more varied in chronic lymphocytic than in chronic granulocytic leukemia the available useful agents are fewer in the case of the lymphocytic form of the disease. They include radiation, certain alkylating agents of the nitrogen mustard type, and the adrenal cortical hormones.

In addition, splenectomy is sometimes of value in the presence of secondary hypersplenic manifestations, most often hemolytic anemia not readily controlled by the corticosteroids.

When a patient suffering from chronic lymphocytic leukemia has conspicuous peripheral adenopathy or if the nodes appear to be enlarging, it is customary to treat with local x-radiation. The tumefaction, as a rule, responds readily to radiation administered in relatively small doses. It is the usual practice at the University of Michigan Hospital to treat each field, of about 10 by 10 cm. size, with single doses of 300 roentgens, although some radiologists employ even lower doses of 200 roentgens or less. More intensive therapy is rarely followed by superior effects and has the decided drawbacks of producing unnecessarily severe systemic reactions and, of greater importance, damaging skin and normal tissues and so limiting future use of an agent for which the indications may be repeated over many years. Total body x-radiation and internal irradiation with radioactive isotopes, notably P^{32}, for the treatment of chronic lymphocytic leukemia have been completely replaced in the writer's practice by the alkylating agents, triethylene melamine (TEM) and P-*bis* (2-chloroethyl) aminophenylbutyric acid (chlorambucil, Leukeran).

TEM, since the first reports of its use as a chemotherapeutic agent in 1950, was the preferred drug for the treatment of chronic lymphocytic leukemia until the recent introduction of chlorambucil. Patients suffering from anemia, thrombocytopenia, hypermetabolism, evidences of intra-abdominal or mediastinal adenopathy, visceral involvement, or extensive infiltration of marrow by leukemic lymphocytes may be benefited by either TEM or chlorambucil. The practice followed by some clinicians of employing drug therapy in essentially asymptomatic patients for "prophylactic" reasons or in the hope of obtaining some subjective benefit has not been adopted by the writer.

TEM is a highly potent agent capable of producing profound marrow depression. Furthermore, the uncertainties of absorption when taken orally and the variable individual responsiveness to its myelosuppressive action increase the need for cautious administration. It is our practice to give 2.5 mg. by mouth, 2 hours before breakfast with 2.0 Gm. of sodium bicarbonate for 1, 2, or 3 consecutive days, depending on the amount of leukemic cell proliferation as estimated by the leukocyte count, and the degrees of adenopathy, splenomegaly, and bone marrow involvement. No further medication is given for 4 weeks, when another dose of 2.5 mg. is usually administered. Some patients receive 2.5 mg. every 4 weeks for long periods as maintenance therapy. In others, treatment may be interrupted for an indefinite time. In general, maintenance therapy with TEM is difficult to establish in chronic lymphocytic leukemia.

Chlorambucil, introduced as a therapeutic agent in malignant lymphoma, in 1953, by Galton and associates,[24] is given with greater safety than TEM, but overdosage with this drug may be followed by myeloid depression, which occurs gradually and is readily reversible on discontinuing the medication.[25] The usual initial dose range, based on body weight, is 0.1 to 0.2 mg. per kilogram per day. If maintenance therapy is planned, a daily dose of 2.0 to 4.0 mg. is usually well tolerated. In the series reported by Doan and associates,[26] the initial dose

of chlorambucil in most patients with chronic lymphocytic leukemia was 0.2 mg. per kilogram per day for 3 to 4 weeks. This was usually followed by a maintenance dose of 2 to 6 mg. daily or triweekly.

It is not yet possible to evaluate the place of chlorambucil with respect to length of remissions or survival in chronic lymphocytic leukemia. However, experience gained in treating 18 patients with this disease for periods up to 24 months at the Simpson Memorial Institute strongly indicates that except for ease of administration and dosage control chlorambucil has no therapeutic advantages over TEM. Those patients exhibiting minimal or moderate activity of their disease are greatly benefited; those with advanced disease may have some suppression of leukemic cell growth and so derive some palliation.

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ADRENAL CORTICAL HORMONES IN CHRONIC LEUKEMIA

The adrenal cortical hormones occupy a limited but well-defined place in the management of chronic leukemia. Granulocytic leukemia almost always manifests an adverse response to these agents, whereas in lymphocytic leukemia their administration may be followed by a fall in the leukocyte count and regression of adenopathy. These effects, however, are short-lived and the greatest usefulness of the adrenal cortical hormones is in the treatment of symptomatic hemolytic anemia and thrombocytopenic purpura. These manifestations of "hypersplenism" occur in about 10 per cent of patients with chronic lymphocytic leukemia as well as in some cases of leukemic lymphosarcoma and malignant reticuloendotheliosis.[27]

Initial adrenal steroid therapy as practiced by the writer is usually carried out with prednisone or prednisolone by employing doses of 15 mg. every 6 hours, given simultaneously with potassium chloride 0.5 Gm. and a suitable antacid. The diet should be low in salt but need not be severely restricted. After one week of high dosage the amount of the drug is gradually reduced until, in most cases, 5 mg. is taken every 8 hours. In some patients hemolysis or severe thrombocytopenia may be prevented by 5 mg. of prednisone or prednisolone taken every 12 hours.

Other indications for adrenal steroid therapy in chronic lymphocytic leukemia occur in advanced stages of the disease, when profound weakness, anorexia, emaciation, and bleeding develop in association with almost complete replacement of normal myeloid elements by leukemic lymphocytes. In these situations continued administration of relatively small doses of the adrenal cortical hormones may be beneficial.

ANTIBIOTIC AND BLOOD TRANSFUSION THERAPY IN CHRONIC LEUKEMIA

Much of the improved outlook for patients with chronic leukemia, especially for those with the lymphocytic form of the disease, is attributable to the supportive measures which are now available. At the first sign of systemic infection, frequently pneumonitis, it is advisable to administer penicillin intramuscularly, 400,000 units every 12 hours, and streptomycin 0.5 Gm. every 6 hours, after obtaining cultures for antibiotic sensitivity tests.

Since even minor surgical procedures, including dental extractions, are associated with increased risk of local infection, the prophylactic use of a broad-spectrum antibiotic in combination with penicillin is advocated in such situations.

In spite of well-defined indications for their employment in special circumstances, most patients having chronic leukemia do not require blood transfusions until the terminal phase of their illness. When the status of the disease is well differentiated at the time treatment is begun, the erythroid values may be expected to improve with specific therapy, and transfusions should be withheld unless the anemia is so severe as to produce symptoms with slight activity. Patients who are able to maintain their hemoglobin and packed cell volume levels at, or above, 10 Gm. and 30 per cent, respectively, do not require transfusions, and the temporary rises obtained by the administration of blood are of no real benefit to them.

Transfusions have a place as adjunct therapy in the management of patients with chronic leukemia when the following objectives apply.

1. Improvement of hemoglobin levels in those patients who are severely anemic at the time of institution of specific therapy.

2. Maintenance of hemoglobin values at levels sufficiently high to prevent or minimize anginal symptoms in those patients having relative coronary arterial insufficiency.

3. Replacement of blood lost by hemorrhage.

4. Control of bleeding. If hemorrhage is due to secondary "hypersplenic" thrombocytopenia, or if the bleeding is from a local site, transfusions of fresh whole blood may tide the patient over until the hemorrhage may be arrested by other means. For this purpose transfusions of resuspended platelet concentrates, which now have limited availability, are preferable to exclusive dependence on whole blood.

5. Counteraction of the effects on circulating erythroid values of secondary hemolysis until the condition may be controlled by specific measures.

6. Partial correction of anemia in patients who have received overdosage of radiation or a chemotherapeutic agent. Although such eventualities should generally be avoidable by judicious selection of dosage and adequate interval observation, an occasional patient will react in an unexpected manner to initial therapy. More often, the distinction between maximum maintenance control and overtreatment may be so fine that in attempting to manipulate dosages to achieve the former, myeloid depression may be produced. We have observed this development most frequently with triethylene melamine in chronic lymphocytic leukemia, but it has also been encountered rarely in patients having chronic granulocytic leukemia receiving either TEM or Myleran. Permanent ill effects of such overtreatment, when recognized early, have not occurred in our experience.

7. Maintenance of erythroid values at tolerable levels in patients having advanced disease in whose marrow there is little remaining erythropoiesis. Such an outcome is not infrequent in chronic lymphocytic leukemia, even in the presence of relatively good preservation of function of other organs. Two or three 500 c.c. transfusions at monthly intervals are usually sufficient to maintain hemoglobin levels between 7 and 10 Gm. per 100 c.c., sometimes for a year or longer.

SUMMARY

One thousand one hundred and seventy-nine cases of leukemia in persons over the age of 13 years seen at the Simpson Memorial Institute of the University of Michigan, from 1927 through 1956, have been reviewed.

Seven hundred and thirty-four cases were classified as chronic and 455 as acute.

The ratio of acute to chronic cases has shown a steady rise during the period studied so that the incidence of acute leukemia seems to be definitely increasing.

The incidence of all forms of chronic leukemia is probably increasing but the nature of the case selection in the present study precludes proof of this thesis.

There is no evidence afforded by this series of cases that the relative frequency of chronic granulocytic leukemia and chronic lymphocytic leukemia is changing, or that there has been any change in sex distribution or age incidence in the chronic leukemias.

Ionizing radiation continues to be the standard of reference when new forms of treatment for chronic leukemia are proposed, and it has not been conclusively demonstrated that survival times are increased or even equaled by the use of drugs in comparison with x-radiation or radioactive phosphorus. Nevertheless, chemotherapy has largely supplanted radiation in the treatment of chronic granulocytic and lymphocytic leukemias in this institution in recent years. With the passage of time and the enlargement of experience, the use of these therapeutic modalities has received increasing justification.

The alkylating agents, Myleran, TEM, and chlorambucil, are the preferred forms of drug therapy for chronic leukemias.

There is no evidence of a qualitative difference in biologic actions of these compounds, but there are quantitative variations which affect dosages, absorption rates, duration of effects, and likelihood of severe myeloid depression.

At the present time, because of advantages of administration, dosage control, and relative safety, Myleran is generally preferred in chronic granulocytic leukemia and chlorambucil in chronic lymphocytic leukemia.

Continuous drug administration on individually determined maintenance dosage has proved superior to intermittent courses of therapy in controlling activity of the leukemic process.

Colcemide may be useful in some cases of advanced proliferative granulocytic leukemia and the antimetabolite, 6-mercaptopurine (Purinethol) may be employed in these situations.

The adrenal cortical steroids are mainly of value in controlling secondary hemolysis and thrombocytopenia which occur in some patients with chronic lymphocytic leukemia and malignant reticuloendotheliosis. When satisfactory control of these manifestations cannot be established or maintained by hormonal therapy, splenectomy may be effective.

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THERAPY OF ACUTE LEUKEMIA IN ADULTS

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INTRODUCTION

ACUTE leukemia is seen in all age groups with about half of the cases occurring in persons who are over the age of 15.[1] When the figures are expressed in terms of the incidence per million population in a given age group, the incidence is as high or higher above the age of 50 as under the age of 20.[2] The incidence of all types of leukemia is increasing, and there are now an estimated 11,000 new cases of leukemia in the United States each year[3] with 9,841 deaths certified from this cause in the United States in 1952, 9,918 in 1953, and 10,443 in 1954.[4]

The diagnosis of acute or subacute leukemia is a morphologic one and is dependent upon the invasion and at least partial replacement of the marrow by a predominant type of immature leukocyte (myeloblast, promyelocyte, monoblast, lymphoblast, or undifferentiated blast). In most cases, this finding is associated with sudden onset and rapid progression of symptoms. A review of the literature[5] indicated that 50 per cent of a group of 577 patients (both adults and children) who were treated only with supportive therapy (transfusion and antibiotics) or supportive treatment and therapy which is now generally thought not to affect acute leukemia (x-ray, P^{32}, urethane, or Fowler's solution) survived 4 months. A group of 56 adults with acute leukemia treated at Memorial Center from January, 1948, to January, 1952 (when the treatment used consisted of the folic acid antagonists and/or the adrenal steroids and ACTH) showed a median survival time of 6 months. A recent survey of a group of patients over the age of 50 with acute leukemia[6] suggested that symptoms initially might be insidious and slowly progressive in these individuals. Once the symptoms were sufficient to require medical attention, and the diagnosis was established, the course was brief.

The management of patients with acute leukemia involves both "specific" and supportive measures. The use of "specific" antileukemic therapy with resultant temporary hematologic remissions (and consequent clinical well-being) is the most the physician has to offer at present. In adults the remission rate is relatively low. Supportive treatment, therefore, aimed at handling the various

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problems as they arise is an important adjunct to the antileukemic agents. The major problems which require treatment are bleeding, the presence of anemia even in the absence of bleeding, and the low resistance to infections of all types. Fever occurs even in the absence of evident infection. In some instances localized leukemic tissue causes symptoms due to infiltration or pressure. This occurs with mediastinal adenopathy, intracranial or intraspinal pathology, or oral or ocular involvement. Bone pain may be severe. Death of the patient with acute leukemia is usually attributable to bleeding or to infection, although there are cases in which no one specific event can be implicated.

Complete, partial, and clinical remissions have recently been defined quantitatively[7] in an attempt to standardize reports of the results of therapy. Complete remission, by definition, implies reversal to normal both hematologically and clinically. The marrow findings in partial remissions may differ numerically, slightly or markedly, from those in complete remissions. Frequently, however, complete or almost complete return to normal of the peripheral blood and clinical pictures accompanies such partial marrow remissions. The incidence in adults of such remissions occurring spontaneously or without the use of specific antileukemic agents is low. Clinical remissions are those in which there is definite symptomatic improvement but the marrow findings and/or the peripheral blood abnormalities and/or the physical signs are not definitely improved.

ANTILEUKEMIC THERAPY

The agents available for the therapy of acute leukemia are as follows: (A) antimetabolites: (1) purine antagonists, (2) folic acid antagonists, and (3) O-diazoacetyl-L-serine (Azaserine); (B) adrenocortical steroids and ACTH; and (C) irradiation (localized).

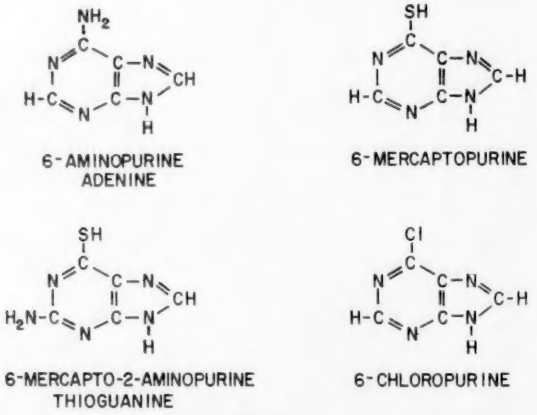

Fig. 1.

Antimetabolites.—

Purine antagonists: Three purine derivatives, 6-mercaptopurine (6MP), thioguanine, and 6-chloropurine (6CP) have been found useful in the treatment of acute leukemia[8-10] (Fig. 1). These compounds presumably affect incorpo-

ration of purines into nucleic acid although the site of action in humans has not been pin pointed. In animal and microbiologic work there is cross sensitivity or cross resistance to these three compounds.[11-13] In the treatment of children with acute leukemia, all three have proved equally useful.

In adults, 6MP and 6CP have been used more extensively. Although the results in the treatment of acute leukemia in adults with 6MP have not been as impressive as in children, this was the first agent to produce remissions in the older age group (over 40 years) with even some regularity. It appears that 6CP is at least as useful as 6MP. Because of this and because of the relatively long remissions occasionally obtained (by comparison with those seen after the adrenocortical steroids), either 6MP or 6CP is the initial agent of choice in treating adults wherever possible. Unless the patient is acutely ill at the start of therapy, requiring the use of steroid because of the need for rapid effect, the purine antagonist is best given alone and continued until a remission occurs or signs of toxicity necessitate temporary cessation of therapy.

6MP is available as a 50 mg. scored tablet. The drug can be given at any time of the day and the entire day's dose is usually given at one time. The usual starting dose is 2.5 mg. per kilogram per day. Although a period of 2 to 4 weeks may be necessary for an initial effect to be noted, in patients with high initial leukocyte counts, the leukocytes may decrease precipitously after only 5 or 6 days of treatment. For this reason it is necessary to follow such patients carefully with daily blood counts. Others need have a blood count only twice a week. It is also important to remember that there is a lag of 3 to 4 days during which a continuing drug effect may be noted after the last dose of 6MP. When the leukocyte count is falling rapidly, administration of 6MP is discontinued temporarily but is restarted as soon as the count stabilizes. If the leukocyte count is falling, but not very rapidly, administration of 6MP is continued. It is also continued at full dosage when leukopenic levels are reached (or in the patient with an initial leukopenia) as long as the marrow remains cellular. Thus, weekly marrow aspirations are often a necessary adjunct to the proper initial use of 6MP. If a patient shows no response to therapy after a 4-week period of treatment and the marrow continues to be hypercellular, the dose of 6MP should be increased to 3 to 5 mg. per kilogram per day.

In a patient showing a favorable response to 6MP, the first sign of change is usually to be found in the marrow. Accompanying a decrease in marrow cellularity, there is a decrease in the percentage of blast cells seen. Before a rise in the numbers of normal granulocytic elements occurs in the marrow, there is frequently a marked increase in the percentage of nucleated red cells. These may comprise as much as 50 or 60 per cent of the nucleated marrow elements in the course of the development of a remission. These nucleated red cells occasionally appear abnormal, resembling the megaloblastic series seen in pernicious anemia or after administration of the folic acid antagonists. The abnormality may persist for weeks after the 6MP is discontinued.

While the peripheral leukocyte count is still falling, or while the patient is leukopenic, improvement in the platelet count and in the peripheral differential may be seen. Rise in the hemoglobin level appears later. As normal

white cells appear in the circulation, the count frequently rises to normal levels despite continued administration of 6MP. Decrease in adenopathy and hepatosplenomegaly does not usually occur until the differential improves. Remissions have occurred from 3 to 13 weeks after the onset of treatment. In the majority of cases the remissions are preceded by some degree of marrow hypocellularity with normal cellularity returning as the normal marrow elements appear. It is therefore important to continue administration of 6MP as long as possible despite apparent lack of effect. If the patient is not getting worse rapidly and is not showing a marked bleeding tendency, 6MP should be continued at least until a hypocellular marrow results.

It is important to continue maintenance therapy with 6MP during the period of remission to prevent rapid relapse, and the maintenance dose is usually the same as the dose required to produce the remission. When the predominant circulating cells are mature ones, it is frequently possible to continue this dose (2.5 mg. per kilogram per day) for months without producing marrow or peripheral blood depression. A blood count should be done every 1 to 2 weeks while the patient is in remission. It is also useful to do a marrow aspiration at least every 4 weeks since a marrow relapse usually occurs before the peripheral blood or the clinical relapse. Knowledge of an impending relapse may enable a different type of therapy to be started in sufficient time for a good effect to be obtained. When the patient begins to relapse while receiving adequate 6MP, a second remission usually cannot be obtained by increasing the dose of 6MP. When 6MP administration is stopped during the period of remission, a second response occasionally occurs with reinstitution of therapy. This does not seem to prolong the total period of remission, however, and may involve an additional period of poor clinical condition for the patient.

Complete remissions following 6MP therapy have been reported by a number of authors to occur in about 15 per cent of the cases treated and partial remissions in an additional 20 per cent.[9] Reanalysis, according to the criteria cited earlier[7] of a group of patients treated at Memorial Hospital, showed 4 complete, 16 partial, and 8 clinical remissions among 58 adults who received 6MP for at least 3 weeks. Among 22 adults treated with 6CP for more than 3 weeks, there were 3 complete, 8 partial, and 4 clinical remissions. In both of these groups complete peripheral blood and clinical responses were observed in many of the patients with partial marrow remissions.

Hall and associates[14] reported somewhat better results in adults treated with larger daily doses of 6MP. It may be that this finding, as well as the possibly better results with 6CP cited above, reflect only the fact that the relative doses used were larger and that temporary marrow hypoplasia was obtained in more patients. Since occasional patients show great sensitivity to 6MP, we prefer to start with 2.5 mg. per kilogram per day and then increase the dose if necessary.

Both complete and partial remissions have been observed in adults of all ages. There does not seem to be any relationship between the occurrence of remission and the type of acute leukemia or the initial level of the white count. The purine antagonists have not seemed to accelerate the course in any patient.

The remissions obtained in adults with 6MP and 6CP have lasted from 2 weeks to 1 year.

The chief toxic effect of the purine antagonists in nonleukemic patients is the depressant action on the bone marrow. This, however, is rarely a problem in the treatment of patients with acute leukemia. A few patients with chronic granulocytic leukemia treated for prolonged periods (6 to 18 months) with 6MP, thioguanine, or 6CP developed anemia and/or thrombocytopenia which cleared when the drug was discontinued. We have not seen this in acute leukemia. As noted previously, the presence of leukopenia, thrombocytopenia, or anemia prior to therapy is not a contraindication to the use of 6MP or 6CP in the treatment of acute leukemia where the marrow is hypercellular or normocellular.

Anorexia, nausea, and vomiting are occasionally noted in patients receiving 6MP and occur more frequently with 6CP. These symptoms can sometimes be decreased by dividing the daily dose into 3 portions given over the course of the day. If this does not control the symptoms it may be necessary to decrease the dose. These symptoms do not indicate a need for stopping the drug (as long as the patient can tolerate it) since they do not presage further toxicity (as is the case with the folic acid antagonists). Oral lesions are rare in the course of treatment with these agents.

It has been difficult to relate the development of jaundice definitely to therapy. In the group of 35 adults with acute leukemia treated with 6CP, however, the 25 per cent incidence of jaundice seen during or after therapy is considerably higher than would have been expected in untreated patients. The jaundice was hepatocellular in type.

Occasional leukemic patients, notably those with high leukocyte counts and bulky lymphadenopathy and hepatosplenomegaly develop hyperuricemia during the course of therapy with the purine antagonists. The situation is analogous to that observed with the adrenal steroids and the polyfunctional alkylating agents. With hyperuricemia, uric acid crystalluria and renal blockage may result.

Folic acid antagonists: Since less than 5 to 10 per cent of the adults with acute leukemia treated with the folic acid antagonists develop complete remissions, as compared with 30 to 50 per cent in children,[15,16] in recent years these agents have rarely been used in patients over 15 years of age.

Elion, Singer, and Hitchings[12] have shown that a strain of *L. casei* made resistant to 6MP shows increased sensitivity to Methotrexate (amethopterin) (4-amino-N^{10}-methylpteroyl-glutamic acid). Law[13] has also demonstrated that strains of mouse leukemia that have developed resistance to the purine antagonists show increased sensitivity to the folic acid antagonist Methotrexate. In the course of study the effects of 6MP we found that we had a group of patients who had become resistant to 6MP but who had not yet become ill enough to warrant starting steroid therapy. At the time that these patients showed definite evidence of relapse in the bone marrow aspirates but only the beginnings of clinical and peripheral blood relapse, Methotrexate therapy was instituted. Unexpectedly several such patients developed complete or partial remissions. These observations are being extended, therefore, to a larger group of cases. Methotrexate is also being given to adults who have received 6MP without

developing a remission and to adults who have developed resistance to adrenal steroids. If these findings of unexpected response to Methotrexate are borne out by further experience, the most logical explanation would be that an alteration of the metabolism of the leukemic cell had occurred under prolonged 6MP administration which caused greater sensitivity to folic acid antagonists. The observation might also be explained, however, on a simple selection of cases, in that the 6MP-sensitive patients may also be the antifolic-sensitive patients.

The folic acid antagonist of choice is Methotrexate because of the relative ease in handling it and the slightly wider zone existing between the amount required for a therapeutic response and the amount producing toxic effects. As indicated above, Methotrexate is not used as the initial treatment in acute leukemia in adults but is reserved for the time that the patient has become resistant to the purine antagonists or to both these and the steroids.

Methotrexate is given orally and the usual starting dose in adults is 5 mg. daily. If this dose is tolerated well without either therapeutic or toxic effects occurring in 4 or 5 weeks, the dose is gradually increased. If, however, toxic symptoms appear first, the drug is stopped temporarily. When the signs of toxicity have cleared, the drug is restarted at a slightly lower dose. It is important to emphasize that frequently the patient must be followed through several periods of toxicity for several months before a remission occurs. Since these patients are already resistant to 6MP, Methotrexate is therefore continued for as long a period as possible, stopping only if rapid worsening with bleeding indicates the need for steroids. Following the production of a remission in these adults, maintenance therapy with Methotrexate has been used.

Toxic manifestations, indicating a need to stop therapy temporarily, include:

1. Mouth lesions. These may be seen anywhere on the lips or the oral mucosa and appear as white or yellow ulcerations surrounded by an area of erythema. Since their development may presage the development of similar ulcerations in the lower gastrointestinal tract, the early detection of such mouth lesions is important. Patients being followed on an ambulatory basis are warned to inspect their mouths daily before taking any Methotrexate. Anorexia, abdominal cramps, nausea, and vomiting may occur at the same time as or shortly before the onset of oral toxicity. All of these phenomena usually precede the development of leukopenia by several days.

2. Diarrhea. This may indicate the presence of intestinal ulceration and the onset of diarrhea should lead to immediate cessation of Methotrexate.

3. Bone marrow depression. The presence of leukopenia, thrombocytopenia, or anemia so frequently seen in acute leukemia is not a contraindication to the use of Methotrexate. It is frequently difficult, however, to distinguish between these signs of the primary disease and the similar effects produced by the drug. If the leukocyte count is falling rapidly, Methotrexate should be discontinued for several days. Treatment can be continued in the presence of leukopenia as long as the marrow remains cellular.

Other results of prolonged administration of folic acid antagonists, such as alopecia and skin pigmentation, are rare and not serious contraindications to further therapy.

Although the simultaneous administration of citrovorum factor and Methotrexate can prevent the toxic manifestations of the latter, it will also prevent any antileukemic effects. If citrovorum factor is given immediately after the dose of Methotrexate, it may also prevent the development of toxicity and so may be useful where an overdose of Methotrexate has been given in error. There is no good evidence, however, that citrovorum factor can speed up the rate of recovery from Methotrexate toxicity once this has developed unless more Methotrexate has been given in the past 24 hours.

Methotrexate is excreted rapidly by the kidneys with 60 per cent of the administered dose appearing in the urine in 24 hours.[17] In the presence of impaired renal function, as evidenced by an elevated blood urea nitrogen, measurable amounts of Methotrexate persist in the blood for prolonged periods and drug toxicity appears sooner. In such patients greater care must be taken in giving this drug.

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Azaserine: Azaserine (O-diazoacetyl-L-serine)[18] when given alone has produced, at best, only brief partial remissions both in children and in adults. There is a suggestion that azaserine given to children in combination with 6MP, however, may produce longer remissions than 6MP alone.[19] Such an additive effect has not been noted, however, in adults with acute leukemia treated with this combination of agents.

Adrenocortical Steroids and ACTH.—The therapeutic responses of acute leukemia in adults treated with ACTH, cortisone, hydrocortisone, or prednisone are poorer than those observed in children. This finding may be related to the apparent difference in response of acute lymphoblastic, myeloblastic, and monocytic leukemias and to the greater incidence of myeloblastic and monocytic forms in adults. A review of the literature[19] has shown that in 425 cases of acute leukemia (including children and adults) there were 5.5 per cent complete remissions in cases classified as myeloblastic, 3.9 per cent in the monocytic, 27.3 per cent in the lymphoblastic, and 42.5 per cent in the "acute" (undifferentiated). Even when data on acute lymphoblastic leukemia are compared, however, the percentage of remissions in children is higher than in adults.[21] In adults over the age of 30, complete remissions are rarely achieved with adrenal steroids. In young adults hematologic remissions occur in about 20 to 25 per cent of the patients treated with cortisone or ACTH. Aggravation of the clinical and hematologic picture has also been noted in cases of myeloblastic and monocytic leukemia in the course of steroid therapy.[20,21] This is not a complete contraindication to the use of the steroids in these types of leukemia, however, since occasional remissions have been obtained which do not vary in completeness or duration from those seen in lymphoblastic leukemia.

In the course of treating with any of the adrenal steroids, the first result to be noted is frequently a precipitous fall in the total leukocyte count to leukopenic levels. This may occur within the first week of therapy and is most marked in those patients with greatly elevated counts at the start of therapy. This response is noted regardless of whether the hormone produces a remission or not. In patients leukopenic before therapy, leukopenia persists and often becomes even more marked. An exception to this is noted in some of the patients

with myeloblastic or monoblastic leukemia in whom administration of the adrenal steroids causes a rapid rise in the leukocyte level.

Shortly after the start of steroid therapy there is often also a decrease in the bleeding tendency even before any platelet rise is noted. Such a decrease in bleeding is transient in those patients who do not show hematologic improvement.

Complete remissions associated with steroid therapy usually are evidenced in the third or fourth week of such treatment although disappearance of fever and subjective improvement may occur much earlier. Improvement in the marrow differential usually precedes peripheral blood improvement. As mature cells appear in the peripheral blood, the white cell count rises from leukopenic to normal levels despite continuation of therapy. The duration of such remissions varies considerably but is relatively brief (averaging approximately 5 weeks).[1] Maintenance therapy does not appear to be particularly successful in preventing this relatively rapid relapse, and for that reason we prefer giving a short course of steroids to initiate a remission and continuing with the antimetabolites as maintenance therapy.

As noted above, the incidence of remission due to steroid therapy seems to be related to the age of the patient, with relatively few over the age of 30 responding to this treatment. The incidence of second remissions in adults is even lower. Despite this lack of response in the older adults, almost all cases seen by us receive adrenal steroids at some point because of the possibility of decreasing bleeding even temporarily.

The preparations of the adrenal steroids used include ACTH given intravenously, ACTHAR Gel intramuscularly, hydrocortisone intravenously, or cortisone, hydrocortisone, or prednisone by mouth. Because of the rapidity of effect following oral administration and the lag noted when cortisone is given intramuscularly, the latter route is rarely used. When the drug cannot be taken by mouth, the need for immediate action is usually great enough to warrant giving it intravenously. We have not noted any difference in the effect of these various agents when given in adequate amounts, other than a slightly more rapid initial response in acutely ill patients given intravenous ACTH. The dose of intravenous ACTH in adults is usually 50 mg. given by continuous drip over the 24-hour period. That of cortisone is 300 mg., hydrocortisone 200 mg., and prednisone 100 mg. daily orally, each divided into 4 doses at 6-hour intervals. The salt intake of the patients is limited when receiving any of these drugs except prednisone, but in adults we have not routinely given potassium chloride, using this only when hypokalemia is present. Hypercorticism of a degree requiring reduction of the dose or discontinuation of therapy occurs only rarely in adults.

Because of the small percentage of remissions in adults and the short duration of the remissions that do occur, it is preferable not to use steroid therapy as the initial therapy in adults with acute leukemia unless the patient is acutely ill. If, however, the patient is not in good enough condition to be carried on supportive therapy for the longer period of time that it usually takes for antimetabolites to be effective, steroids become necessary. Thus, in patients with

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a marked bleeding tendency or a rapidly rising leukocyte count at the time of diagnosis, adrenal steroid therapy is indicated as initial treatment. It is also indicated in patients who have become resistant to antimetabolites or who show signs of a rapid downhill picture in the course of a trial of antimetabolites. Steroids are also used where rapid shrinking of tumor masses is necessary as in the case of the development of paraplegia or of mediastinal involvement.

There is little to suggest that prednisone in amounts equivalent to the usual cortisone dose has any greater therapeutic effect, but there is definitely less disturbance of electrolytes. There are some indications, however,[22,23] that prednisone given in the massive dose of 1 Gm. daily can produce good remissions in patients not usually considered responsive to adrenal steroids, i.e., those over the age of 30. Hill and his colleagues found that 5 of 19 patients over 30 had complete remissions, 1 a good remission, and 2 had partial remissions. In addition, repeated responses have been observed in such patients. In a group of 15 adults treated at Memorial Hospital with 1 Gm. or more of prednisone daily, however, only 1 remission followed. This same patient subsequently responded to 100 mg. of prednisone daily. Most of the patients in our series were late in the course of their disease and many were known to be resistant to smaller doses of the adrenal steroids.

Irradiation.—X-ray therapy does not have a place in the over-all treatment of acute leukemia similar to its role in chronic leukemia. Spray irradiation or treatment of an enlarged spleen or liver not only does not benefit the patient, but has, on occasion, seemed to precipitate a more rapid downhill picture associated with bleeding.

There are situations, however, where localized x-ray treatment in small doses is useful. For the most part this is true where symptoms result from local adenopathy or tumor masses such as spinal cord or brain involvement or mediastinal or abdominal adenopathy. Bone and joint pain due to acute leukemia will also respond to small localized doses of x-ray.

Nitrogen mustard and other radiomimetic substances such as triethylene melamine, Myleran, and triethylene thiophosphoramide as well as other marrow depressants such as urethane and Fowler's solution are not generally useful in the treatment of acute leukemia. Neither hematologic nor clinical remissions occur although leukocyte depressions can be obtained readily and brief subjective improvement occasionally results.

CHILDHOOD LEUKEMIA

Since this paper is written mainly for internists, the discussion has been, so far, limited to the treatment of the adult patient with leukemia. It would seem worth while, however, also to mention briefly the disease in children, although this has been reviewed recently in considerable detail in a similar paper.[19] The disease in children is preponderantly of the lymphoblastic or undifferentiated stem cell type, although acute granulocytic, myelomonocytoid and monocytic forms are seen occasionally. The forms of treatment available are much the same as those available in adult acute leukemia, but the response is, in general, better in children than in adults. With the folic acid antagonist, Methotrexate,

at an average dose for a 5-year-old child of 2.5 to 5 mg. daily by mouth, one can expect complete remissions in approximately 30 per cent and definite clinical improvement in about 50 to 60 per cent of the patients. Similarly, with 6MP at 2.5 mg. per kilogram daily by mouth, 30 to 50 per cent complete remissions can be obtained. There is a suggestion that the combination of 6MP and azaserine at 2.5 mg. per kilogram of each drug daily by mouth is more effective than 6MP alone, both in the number of remissions achieved and in the length of these remissions. Comparison of these two regimens in the treatment of patients is under way at present in 12 clinics throughout the country, and definite knowledge of the value of the combination should be available in another 6 months. The adrenal steroids are useful in the treatment of acute leukemia in childhood. ACTH by constant intravenous drip probably acts more rapidly than any other form of treatment and is useful in the acute emergencies. Among the adrenal steroids, we prefer prednisone 40 to 50 mg. daily given in divided doses every 6 hours. It is our feeling that the steroids are extremely useful agents in the treatment of acute leukemia and will work rapidly when the antimetabolites would not have time to exert their beneficial effects. In any patients who are not acutely ill, we feel that it is better to employ the antimetabolites and that the steroids should be reserved for such times when they and they alone can act with sufficient rapidity to save the patient.

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SUPPORTIVE THERAPY

Although this therapy is nonspecific, it is of prime importance in treating patients with acute leukemia. As in any other illness it is extremely important to treat vigorously any of the general medical or surgical complications which may arise.

Since these patients are prone to develop infections, antibiotics are important adjuncts to treatment. They should not be used prophylactically, however, even in the face of a low leukocyte level because of the further problems of generalized moniliasis or of the emergence of resistant strains of bacteria with such use. With specific infections, the appropriate antibiotic should be used. When no cause for the fever can be found, a therapeutic trial of a broad-spectrum antibiotic is indicated.

Transfusions are extremely important in maintaining the comfort of these patients. Most patients with acute leukemia are anemic when first seen or develop anemia shortly thereafter. If the hemoglobin is falling rapidly (with or without bleeding) or if the hemoglobin level is low enough to cause symptoms, transfusions are indicated. If the hemoglobin level is above 9 Gm. per cent, transfusions are not usually necessary unless the patient is actively bleeding. Direct transfusions are not of any greater benefit than indirect transfusions in treating the anemia.

Neither overt acquired hemolytic anemia nor a positive Coomb's test is usually seen in acute leukemia and there is rarely any difficulty in cross matching the blood for transfusions for these patients. As in other diseases where frequent transfusions are required, febrile reactions occasionally occur after transfusions without hemolysis or other evidence of transfusion incompatibility.

As in any acutely ill patient, attention must be given to the fluid and electrolyte status. It should also be remembered that a surgical procedure is not necessarily contraindicated in these patients even when in relapse. Adequate drainage of infections, where possible, is important. Complications unrelated to the primary disease such as acute appendicitis, intussusception, renal calculi, and intestinal obstruction have been seen. Surgical intervention may be temporarily life-saving.

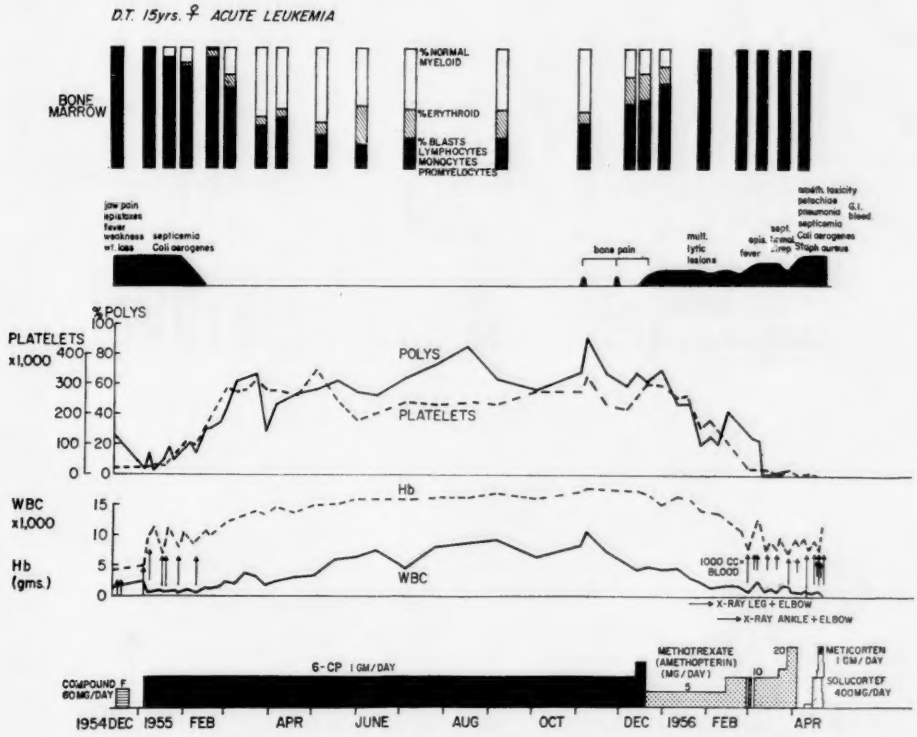

Fig. 2.—This chart illustrates the use of 6CP despite initial marked leukopenia and thrombocytopenia in the presence of a hypercellular marrow. As the bone marrow improved the leukocyte and platelet counts rose to normal. The patient had a prolonged remission. Bone pains appeared at the same time that the marrow relapsed, 1½ months before there was peripheral blood relapse and osteolytic lesions were found by x-ray. There was brief symptomatic improvement following irradiation of the bone lesions. There was no response to Methotrexate or prednisone. The patient died following episodes of septicemia and hemorrhage.

When an operation is necessary in the acute leukemic patient with a bleeding tendency, there are several adjuncts to therapy that may decrease bleeding temporarily. Although platelet transfusions rapidly lose their effect when given repeatedly in the routine treatment of acute leukemia, the first 1 or 2 such transfusions are useful. Recent use of stored, frozen platelets[24] gave repeated responses in several patients bleeding because of acute leukemia. A similar effect can be obtained by giving a transfusion of freshly drawn blood that has been collected in a plastic bag, coagulation being prevented by the removal of calcium by an ion exchange resin.

Temporary decrease in the bleeding tendency, sufficient to permit a surgical procedure, can also frequently be obtained by treatment with adrenocortical steroids.

In the course of treating patients with acute leukemia, we attempt to keep their periods of hospitalization to a minimum. Unless severe bleeding, infection, or weakness is present, these patients often do not need hospitalization and can have their necessary blood counts and transfusions on an outpatient basis.

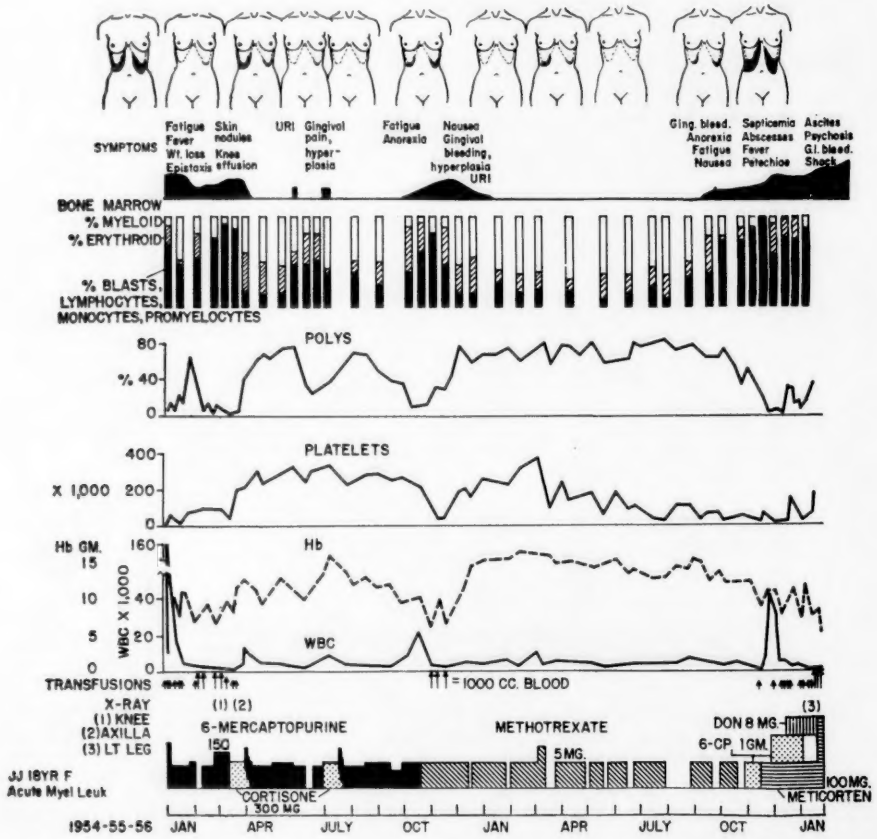

Fig. 3.—This 18-year-old girl with acute myeloblastic leukemia and an initially elevated leukocyte level had a brief partial response to 6MP. While she was relapsing she developed a joint effusion which cleared after x-ray therapy. She then had 2 remissions on cortisone followed by a complete and prolonged remission during treatment with Methotrexate. When resistance to this developed, there was no response to 6CP and only transient decrease in the bleeding tendency when prednisone was given in doses of 100 mg. and 1 Gm. daily. The patient died of gastrointestinal tract hemorrhage.

SUMMARY OF MANAGEMENT OF ACUTE LEUKEMIA IN ADULTS

When a diagnosis of acute leukemia is first made, the patient may be acutely ill with high fever and/or bleeding or, in many other cases, may be ambulatory

with less striking symptomatology. With patients in the second category, the initial therapy of choice is 6MP (or perhaps 6CP). This drug should be given either until a remission results, or until it is no longer possible to continue therapy. This second situation arises with the development of a hypoplastic marrow or the appearance of acute complications of the disease. In only a few cases is further administration of the drug prevented by severe nausea and vomiting. It is important to remember that the production of a remission by 6MP may take as long as 3 months and thus persistence in treatment is necessary and should be supplemented by antibiotics and transfusions when needed.

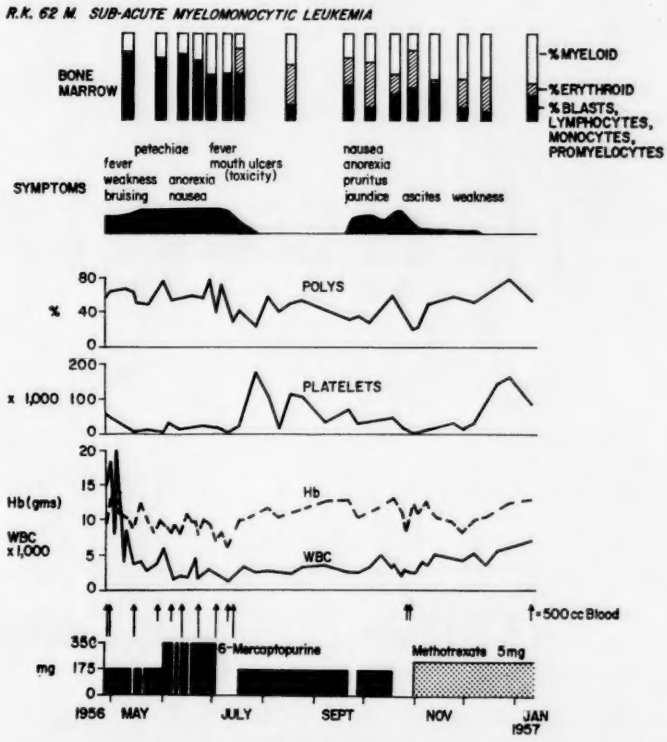

Fig. 4.—This chart indicates the occasional need for prolonged treatment with 6MP before obtaining a response The patient had a hypocellular marrow for a month on continued therapy before erythroid elements appeared. He developed severe oral mucosal ulcerations as a manifestation of 6MP toxicity. Course was complicated by appearance of jaundice with clinical and laboratory findings most consistent with a diagnosis of infectious hepatitis. Since the peripheral blood seemed to indicate the beginning of a relapse, the patient was given Methotrexate, on which he had a partial remission.

If a remission is produced, treatment with 6MP should be continued. When a relapse occurs during the course of treatment, thus demonstrating the development of resistance to 6MP, there is usually nothing to be gained by increasing the dose of the drug since further remissions have rarely occurred in this situation. This is the time to change therapy. Since it is of advantage to change

therapy before the patient is acutely ill, and since relapse is frequently demonstrable in the marrow prior to clinical relapse, serial marrow aspirations during treatment are valuable in handling the case.

Following the demonstration of resistance to 6MP, unless the patient is acutely ill he should receive a trial of Methotrexate. This agent, too, is continued until remission occurs, the patient becomes acutely ill, or resistance to Methotrexate occurs. Unlike 6MP, it is frequently not possible to give Methotrexate to the point of marrow hypoplasia since oral toxicity develops first. Since it may take several months to achieve a remission, it may be necessary to give the drug to the point of oral toxicity several times.

When the patient is considered to be so ill initially that there is not sufficient time for antimetabolites to take effect (minimum of 3 weeks), or is rapidly growing worse while on antimetabolite therapy, or has become resistant to antimetabolites, adrenal steroid therapy is indicated.

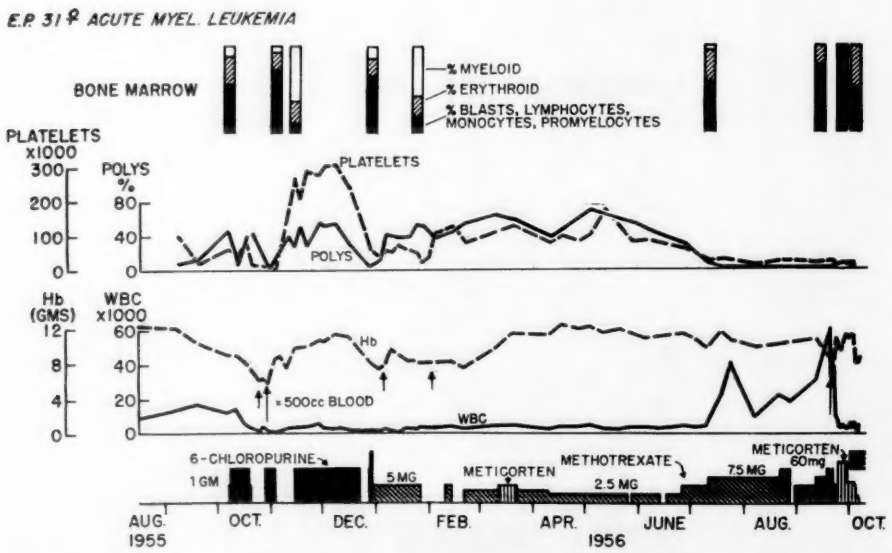

Fig. 5.—This chart shows the course of a 31-year-old woman with acute myeloblastic leukemia who responded well clinically and hematologically to 6CP. When resistant to 6CP, she responded to Methotrexate. Following development of resistance to the latter, she was treated with prednisone. This caused a clearing of fever and increase in marrow erythroid elements but no maintenance of hemoglobin. Prednisone was discontinued because of the development of an acute psychosis. There was no further follow-up.

Figs. 2, 3, 4, and 5 show the course of 4 patients and demonstrate some of the points mentioned.

The median survival time in a group of adults treated at Memorial Hospital prior to the use of the purine antagonists was 6 months. No difference was noted in the group as a whole during the next 4 years when these latter drugs were available. Those patients who enjoyed either complete or partial remission did show an increase in the median survival time to 11 and 8 months,

respectively, but this is not a valid comparison since this is a selected group of patients (who lived long enough to receive adequate trials of the purine antagonists).

Since a much higher percentage of children respond to one or more of the types of chemotherapeutic agents, these responses have been reflected in the increases in survival time in children following treatment. A series of cases, relatively untreated, collected from the literature by Tivey showed 3.9 months survival in the untreated group, and our series of 184 consecutively admitted children with acute leukemia at Memorial Center showed a median survival time of 12.4 months. Although the actual remissions in children to a given agent may be no longer than those achieved in adults, the percentage responding to each agent is much higher in children than in adults.

Not indicated by the adult figures, however, is the fact that any increase in the duration of acute leukemia in an individual case does not usually mean a more prolonged time of illness and discomfort to the patient. These periods of remission are periods of well-being and, in most cases, patients can lead normal lives during remissions. This is not a period of suffering but a period of useful life. The terminal illness is not more severe or protracted than in the untreated patient. When properly used the specific agents should not produce distressing side effects. For these reasons we feel that it is imperative to treat these patients with the antileukemic agents available in addition to using all supportive therapy indicated.

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SOME ASPECTS OF THE LYMPHOMA PROBLEM

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THE acute and chronic diseases that involve the lymphatic tissue are many, and the texts that are devoted to this subject are, of necessity, lengthy (Wintrobe[1]). This report is confined, therefore, to a discussion of only selected aspects of the lymphoma problem.

It might be stated fairly that prior to the last 15 years, patients with Hodgkin's disease, lymphosarcoma, and follicular lymphoma were, primarily, from the point of view of care, of continuing interest to the radiologist. Surgeons saw them first to perform biopsies or dissections of an initial focus, and again only if a surgical emergency arose in the course of the disease; pathologists made tissue diagnoses; and internists and general practitioners saw them only in the diagnostic phases of their disease, or to assist in blood replacements or the management of intercurrent medical complications.

Today there is evidence of widespread interest and enthusiasm in the matter of caring for the patient with lymphoma. This change in attitude is reflected not only in better over-all care but is responsible as well for the patient's having a less gloomy attitude toward his chronic affliction.[2] It is not too far removed from reality to say that the outlook of a patient with a lymphoma is not too different from that of a patient who has just suffered from a coronary occlusion and has recovered.

The reason for this change in attitude on the part of physicians toward the management of these chronic diseases is difficult to determine with any degree of certainty. It can perhaps be traced most easily to the first successful application of chemotherapy to the lymphomas. This historic development begun by Gilman, Goodman, Lindskog, and Dougherty in 1942, and reported in 1946,[3] introduced the nitrogen mustards *tris* (β-chloroethyl)-amine hydrochloride (HN_3) as therapeutic agents for a group of diseases that hitherto were treated almost exclusively by roentgen irradiation. The subsequent addition of the "methyl bis" nitrogen mustard (HN_2),[4,5] triethylene melamine (TEM),[6,7] and p-(N, N-di-2-chloroethyl) aminophenylbutyric acid (CB 1348, Chlorambucil),[8-10] all alkylating agents and derivatives of nitrogen mustards, as adjuncts to x radiation, has immensely amplified the chemotherapeutic approach to the problem. HN_2, TEM, and Chlorambucil, which may be considered of "specific" value, have been supplemented by antibiotics, ACTH, the adrenal steroids, and other agents

that make it possible to maintain lymphoma patients as happier and more useful members of society than would otherwise be possible. Of the three nitrogen mustard compounds now in general use, we prefer HN_2 administered intravenously in most cases; we use TEM most frequently for ambulatory patients in whom definite but minimal evidence of the disease process persists; and Chlorambucil may substitute for TEM in selected cases. All of these cytotoxic agents are marrow depressants. Because of the unpredictability of the bone marrow sensitivity of patients to TEM, we regularly give a test dose of 2.5 mg. and check the patient's blood count, including the platelets, one week later before proceeding with another 2.5 mg. dose. On several occasions, we have found that patients who have tolerated 15 mg. (given in three days) without serious bone marrow depression have subsequently been more sensitive and have had serious hematologic sequelae from the same dose (15 mg.), even though the state of the patient's disease, the peripheral blood, and the bone marrow were apparently unchanged.

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DIAGNOSIS AND PROGNOSIS OF THE LYMPHOMAS

Biopsy and histologic classification are absolute necessities in diagnosing lymphoma because there are a number of disorders that involve the lymph nodes and often simulate the clinical picture of a lymphoma.[11] Even with careful histopathologic study, the immediate diagnosis may be difficult, if not impossible, because of the occasional bizarre "benign" hyperplasia. In this type of problem, the gain to the patient by withholding therapy and observing him closely may be immense. In point of fact, it is in this group that we are most likely to find "cures" among our patients that we have treated unwisely on the basis of a "mistaken diagnosis."

Histologic classification of the type of lymphoma is of great importance in assessing the general prognosis of the patient. But as has been pointed out by Custer and Bernhard,[12] Rappaport and his associates,[13] Craver,[14] and others, this approach may be startlingly inaccurate, since biopsies from different sites in lymph node involvement may show vastly different histologic structure. For example, it is not uncommon in follicular lymphoma to perform another biopsy and find that the node being studied has no follicular pattern. It may be a mistake under these circumstances to assume that the disease has progressed to a lymphosarcoma and requires treatment, because continued observation may show that the disease will continue a benign course, and subsequent biopsy may again reveal a follicular pattern. The clinical state of the patient and his progress do not always correlate with the histologic appearance of the node. A patient with reticulum cell lymphosarcoma may be unusually responsive to roentgen-ray therapy, whereas one with Hodgkin's granuloma may fail to respond adequately to x radiation or HN_2, or to a combination of both of these agents. It is also worthy of note that a relatively benign process may be as serious as an unresponsive, more "malignant" process simply because of the site of involvement. A follicular lymphoma involving the mesenteric or perihepatic nodes may be radiosensitive or may respond to HN_2 or P^{32}, and yet the prognosis may be poor because of complications caused by repeated episodes of intestinal or biliary obstruction or hemorrhage.

An unusual case of Hodgkin's disease that illustrates the difficulty sometimes encountered in assessing the indication for treatment and prognosis is given. This case was described in *The Medical Clinics of North America*[15] in 1947. The patient's subsequent history since this publication is added without quotes.

"J. C., a 24-year-old male clerk, was admitted to Billings Hospital on September 25, 1944. On November 11, 1943, the patient had been hospitalized elsewhere because of epigastric distress of a year's duration and the discovery of lumps in his neck. A biopsy of a cervical lymph node made at that time was reported to the patient to show Hodgkin's disease. In December of 1943, a series of eight x-ray treatments were given to the neck, five to the right axilla, and ten to the abdomen and back, with relief of symptoms and decrease in the size of the lymph nodes. In approximately two months, however, the patient's original complaints recurred and in addition he noted increasing weakness and fatigue. In May, 1944 he began to have recurrent chills and fever.

"On examination the patient was found to have a temperature of 40° C., pulse 100, cervical lymphadenopathy, hepatomegaly, and an anemia. Study of the peripheral blood revealed: hemoglobin 8.9 gm. per 100 cc. (photoelectric); erythrocytes 3,340,000 per cu. mm.; platelets 44,000 per cu. mm.; leukocytes 2,100 per cu. mm.; a prolonged bleeding and clot retraction time, normal clotting time and increased capillary fragility (Rumpel-Leede). The Wassermann and Kahn tests were negative. Examination of the original biopsy specimen revealed typical Hodgkin's disease.

"In view of the leukopenia and thrombocytopenia, it was decided to give the patient only two injections of HN_2 and on October 1 and 2 a dose of 5.7 mg. was injected intravenously. Mild nausea and vomiting followed each injection within three hours. The patient's temperature fell to normal within forty-eight hours after the first injection. Five days after the initial injection, the leukocytes of the peripheral blood had fallen to 875 per cu. mm., of which 744 were neutrophils and 96 lymphocytes. The platelets, however, had risen to 82,000 per cu. mm. Ten days after the initial injection, the leukocyte and platelet values reached 2,000 and 100,000 per cu. mm. respectively, and the bleeding and clot retraction time were within normal limits. Within forty-eight hours after the first injection the patient felt well and within three weeks the lymphadenopathy and hepatomegaly had resolved. The remission produced by this first course of two injections lasted four months. The patient has since received seven courses of therapy with HN_2, each consisting of four consecutive daily injections of 0.1 mg. per kilogram of body weight. Remissions have been from two to five months' duration. The lymphadenopathy and hepatomegaly *have not recurred* since the original treatment. Remissions are terminated by appearance of chills and fever, malaise or leukopenia and thrombocytopenia, or, as has been true on three occasions, by presentation of generalized petechiae of the skin and mucous membranes and bleeding gums with or without accompanying chills and fever. Platelet values before treatment in these instances have been between 30,000 and 40,000 per cu. mm., with a prolonged bleeding and clot reaction time. A course of therapy with HN_2 has been followed promptly by cessation of symptoms, chills and fever, disappearance of petechiae, a return of bleeding and clot retraction time to normal, and a rise in the platelet value to 100,000 per cu. mm. or more. The leukocyte values, which before each course of therapy usually are between 1,800 and 3,000 cells per cu. mm. rise slowly with the induced remission to approximately 4,000 per cu. mm."

After this series of treatments with HN_2, the patient continued to work without recurrence of his disease until 1957. In the interval between 1947 and 1957, he was seen on many occasions as an outpatient with complaints unrelated to Hodgkin's disease. He was admitted for the seventeenth time on April 17, 1957, with the complaints of fever, night sweats, rapid pulse, weakness, and recurrence of adenopathy, all of about two months' duration. Physical examination revealed generalized lymphadenopathy and a spleen palpable at the costal margin. The laboratory examination revealed a moderate normochromic, normocytic anemia (hemoglobin, 10.0 Gm., and red blood count, 3.36 million), and a leukocytosis (white blood count, 31,000). The number of platelets and reticulocytes was normal. The bone marrow was also normal except for a hyperplasia of the granulocytic elements and an increased iron storage. Biopsy of a lymph node revealed it to be a classical Hodgkin's picture having a structure similar to that of Hodgkin's granuloma.

The patient was given a total dose of 0.4 mg. per kilogram of HN_2 in doses divided over a 4-day period. Within a week his temperature returned to normal and the adenopathy and splenomegaly disappeared. He has since been feeling well and has returned to work.

This case is of interest for several reasons. The recurrences in the beginning were characterized by fever, leukopenia, thrombocytopenia, and anemia, and each treatment with HN_2 resulted in a temporary regression in the disease process. This phase of the illness continued over a period of nearly 4 years. Thereafter, the patient remained free of the disease from the standpoint of symptoms and physical or laboratory signs for 10 years.

For the first 4 years that we observed and treated this patient, one might logically question whether he had a "panhypersplenism" with each flare-up of Hodgkin's disease, or whether we were treating a disorder essentially unrelated to Hodgkin's disease. At the time of our initial observation, it would have been foolhardy to suggest anything but a rather gloomy future, and, in a general way, all of the cytotoxic approaches were contraindicated.

After a quiescent period of about 10 years, the disease finally recurred and appeared histologically as it had in the beginning. The fact that the patient had been treated 8 times with HN_2 (exclusively except for the initial roentgen-ray therapy) indicates that, in some cases, the development of resistance to the chemotherapeutic drugs as described by Burchenal[16] may be of minor importance.

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THE NATURAL HISTORY OF LYMPHOMAS

As pointed out by Haut and co-workers[17] and Karnofsky,[18] each case of leukemia or lymphoma has, in a sense, a predetermined pattern that limits what the over-all effect of therapy will be. If therapy is effective, it succeeds only in keeping the patient in a relatively good state of being until he reaches that point inherent in his make-up where therapy fails completely. The statement that is found in the literature repeatedly that x-ray therapy and the chemotherapeutic agents do not in reality prolong the patient's life[14,19] is essentially in agreement with Karnofsky's concept of the natural history of the lymphomas. This concept is analogous to what might be expected in a patient with polycythemia rubra vera. If one keeps the patient from dying of a thrombosis or other complication by phlebotomy and P^{32}, in due time the disease will convert to one of myelofibrosis or leukemia, and nothing can be done to prevent this progression at a time peculiar to the particular individual.

This concept about the course of these diseases has not been proved to be correct. In fact, it is my belief (which is perhaps prejudiced by optimism and naivete) that one has but to watch the lymphoma patients to see evidence that the body under various circumstances may hasten or delay the "relentless progress" of the disease. I am reminded of several children with rapidly progressive Hodgkin's disease, whom we have seen go into a quiescent state at puberty and then require but little therapy for years thereafter. We would not claim that the therapy we gave (x-ray therapy and HN_2) had anything to do with this change, but rather that the body environment at puberty changed sufficiently to alter the host-tumor relationship. What we may occasionally accomplish by therapy is to maintain the patient in a state of well-being that makes it possible for the body to utilize such "defenses." The importance of such "unknown" factors in influencing the course of cancer has been emphasized by Stewart,[20] who has pointed out such occurrences as encouraging avenues of research. In one sense,

the idea that no therapy will prolong life beyond the specific limit for a given individual is discouraging, but nevertheless, we as physicians must use every known means at our disposal to maintain the patient as a useful, productive, and happy member of society as long as possible.

As happens in the case of so many chronic diseases, the patient with lymphoma inevitably reaches a stage in which all therapeutic measures fail, or in which some complication occurs that makes the usual therapy hazardous or contraindicated. The complication, or sequela, of the underlying disease that is most common in our experience is hematologic. This abnormality varies from anemia to pancytopenia, which fails to respond adequately to all routine therapy. In many instances, this is a frustrating situation, since evidence may be ample that the disease is not yet completely unresponsive to cytotoxic agents but only relatively so.

A case that illustrates these concepts about lymphomas and simultaneously demonstrates the general lack of knowledge follows.

About 6 years ago, F. S., a 28-year-old laborer, first noted the appearance of asymptomatic bilateral cervical and axillary lymph nodes. A biopsy at that time revealed a classical Hodgkin's granuloma. Because the patient was asymptomatic, no treatment was given. He was observed at relatively frequent intervals and remained asymptomatic. Three more biopsies were made over the next 5 years, all of which revealed the same characteristic picture. In the sixth year of his disease, he began to have systemic symptoms, including fever, malaise, and weight loss, and, as a consequence, x radiation and HN_2 therapy was instituted. No complete remission was ever achieved, and he died during the sixth year of the disease from the complications of disseminated Hodgkin's disease.

It might be argued that had therapy been instituted at the time of the first biopsy, the disorder might not have progressed to the final stage in the sixth year. If the concept proposed by Karnofsky[18] is correct, however, as far as the patient was concerned, nothing was lost in withholding therapy.

GENERALIZATIONS ON THE THERAPEUTIC APPROACH TO THE LYMPHOMAS

Most physicians would agree that roentgen-ray therapy is, in the over-all sense, the most effective single agent available for the treatment of the lymphomas.[14,21] However, experience over the years has indicated that an appraisal of the condition of the patient and the extent of involvement may dictate whether treatment should be confined to surgery,[22] roentgen irradiation, HN_2, or to a combination of these agents. The rules of thumb, which are probably applied most generally, may be summarized as follows:

1. Initial disease in a single localized focus. Surgical removal of the lymph nodes short of radical dissection, followed by roentgen-ray therapy to the involved and immediately adjacent areas.

2. One or more areas of involvement (too extensive for surgical removal), such as unilateral cervical and unilateral axillary. Roentgen irradiation of the involved areas.

3. Major mediastinal involvement or extradural involvement of the spinal cord or brain. Nitrogen mustards (HN_2) given initially to shrink the tumor and to avoid compression of adjacent structures followed by roentgen-ray therapy to the involved area.

4. Localized or multiple bone involvement. Irradiation of the involved areas is indicated in general, but the degree of involvement may dictate the initial use of HN_2, followed by roentgen-ray therapy, or vice versa.

From the medical students and the younger members of a hospital staff, one not infrequently hears that the nitrogen mustards are useful for treating lymphomas even after the tumors become resistant to irradiation. Few who have seen a large number of these patients would disagree with the fact that those who have had repeated roentgen-ray therapy to numerous sites and still have systemic symptoms may respond to HN_2 or other mustard derivatives. This response is usually transitory but occasionally it is of remarkably long duration. It probably represents the effect of HN_2 on loci of the disease that have not been reached by the roentgen rays rather than a true resistance to the radiation. Although one could theoretically achieve the same result with whole-body x radiation, there are few who would recommend this approach except in highly selected cases. In our experience, the cases in which local lesions fail to respond to roentgen-ray therapy but which respond to HN_2 or its derivatives are rare or nonexistent. On the other hand, further roentgen-ray therapy may be contraindicated because of local tissue conditions at the site of tumor involvement, whereas no contraindication exists for HN_2.[14] In such instances, therapy with HN_2 may produce a satisfactory regression of the tumor and a clinical remission. Thus, contraindication for x radiation does not mean that the tumor has become radioresistant; it is simply referred to loosely as such. If roentgen-ray therapy fails to induce a remission, a trial of HN_2 is always indicated, and vice versa.

A summary of a case is presented here to illustrate the usefulness of HN_2 in patients with active disease but in whom the localization of the focus escapes detection.

M. B. was first seen in 1953, with fever, malaise, and cervical and axillary adenopathy. Biopsy revealed Hodgkin's disease (paragranuloma). He was given localized x-ray therapy. The symptoms disappeared, and he had a complete clinical remission for 1½ years. Since that time he has had recurrences of the disease every 4 to 7 months. Each of these recurrences has been characterized by fever, malaise, loss of appetite, and loss in weight. At no time during these recurrences has he had adenopathy, nor has his spleen enlarged as judged by palpation. Roentgenographic examinations of his chest and gastrointestinal tract have revealed no abnormalities, and cultures of his throat, urine, etc., have been negative. With each recurrence of symptoms we have treated him with TEM (5 mg. × 3) or HN_2 (4 mg. per kilogram). A prompt regression of fever and a return to a state of well-being have followed each course of therapy.

It is logical to assume that each of these episodes is a recurrence of Hodgkin's disease. Undoubtedly, if one waited long enough and allowed the patient to suffer needlessly, the focus might very well be determined as it grew larger and became locally manifest. However, by using HN_2 or TEM, the patient is being maintained in good spirits in an active normal life with a minimum of discomfort. There are among physicians a few who adhere strictly to roentgen-ray therapy, and hence some of their patients may be denied a complete clinical remission.

PREGNANCY AND LYMPHOMAS

Southam,[23] who recently studied the problem of lymphomas and pregnancy, has concluded, on the basis of observations on 59 patients with Hodgkin's disease,

that pregnancy is medically undesirable in a patient with active Hodgkin's disease. The perplexing question of what advice to give women in the child-bearing period is a recurrent one, and it is our policy, in general, to advise against conception. If, however, after the consequences are explained to both husband and wife, they insist on having a child, then it is suggested that the attempt be made only several months after a complete clinical remission has been induced and the patient appears in a good general state. Pregnancy during remission probably has no adverse effect on the occasional patient with Hodgkin's disease, lymphosarcoma, or follicular lymphoma who has a relatively benign course with need for therapy only at infrequent intervals. One such patient under our care who has Hodgkin's disease (paragranuloma) and who has required treatment only every 2 to 3 years over the past 12 years, has had three successful pregnancies. During this interval, the course of the disease has not changed in any way.

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Another patient with lymphosarcoma (lymphocytic type) became pregnant 3 months after diagnosis and after initial roentgen-ray therapy had been applied to a huge mediastinal and a single small supraclavicular focus. Gestation proceeded without complication. Recurrence of the disease in cervical and axillary foci was noted 2 years after the initial treatment and one year after childbirth. Roentgen-ray therapy was given to these areas, and the patient is still in remission 2½ years after the second exacerbation.

Many similar examples could be given of successful pregnancies without apparent adverse effect on the patient. In view of Southam's[23] data and of the inability of the physician to predict the length of a remission in the average case of lymphoma, pregnancy should be discouraged except in those patients in whom a relatively benign course has been ascertained by observation.

In the event that active disease occurs during pregnancy, or that pregnancy occurs when the disease is already active, management will depend on the site and extent of involvement and on whether systemic symptoms are minor or major. In some it may be possible to postpone treatment until after childbirth; in others, nitrogen mustards,[24] local irradiation, or even local surgical resection may be indicated.

RADIOACTIVE ISOTOPES IN THE TREATMENT OF LYMPHOMAS

Of the many radioactive isotopes available, only radiophosphorus (P^{32}) has been of any value in the management of the lymphomas. This isotope, which has a differential affinity for lymphatic tissue, is probably never, in our experience, indicated in the treatment of Hodgkin's disease[14] but may be effective in the management of selected cases of follicular lymphoma[15,26] and lymphosarcoma. In general, however, effective remissions are obtained more consistently by means of roentgen-ray therapy or the nitrogen mustards.

INDICATIONS FOR THERAPY OF LYMPHOMAS

Honest difference of opinion exists concerning indications for therapy for lymphomas. There are those who treat patients with asymptomatic follicular lymphoma and those who treat recurrences of Hodgkin's disease and lympho-

sarcoma even though the patient is free of systemic signs or symptoms. The more conservative approach that we follow is not to treat follicular lymphoma unless the lymphatic involvement is producing local or systemic symptoms sufficient to warrant intervention. In Hodgkin's disease and lymphosarcoma, with rare exception, we always direct treatment toward the initial disease and we seldom treat patients with recurrences until we are satisfied that the process is gaining impetus and is producing systemic symptoms. We have been struck by the frequency with which a flare-up in a single small focus produces local or systemic symptoms for only a brief period and then subsides spontaneously in a week or more, remaining apparently dormant for varying periods of time.

THE USE OF ADRENAL STEROIDS IN LYMPHOMATA

As in chronic lymphatic leukemia, one not infrequently encounters overt autoimmune hemolytic anemia in patients with lymphoma that responds dramatically to ACTH and the adrenal steroids.[27] The case of Hodgkin's disease described here illustrates this fact.

R. B. developed a lymphadenopathy, fever, and malaise in 1952. Biopsy of a cervical gland revealed Hodgkin's disease. He was given x-ray therapy to the cervical gland, and mediastinal involvement and a complete clinical remission occurred. In 1954, the patient again developed fever, cervical adenopathy on the side opposite to that first involved, an enlarged spleen, and a normochromic, normocytic anemia. Decreased erythrocyte survival, an active erythroblastic bone marrow, an increased number of reticulocytes, increased fecal urobilinogen excretion, and a positive Coombs test demonstrated the presence of an acquired hemolytic anemia. The patient was treated with a course of HN_2 and given cortisone (100 mg. per day). The nodes disappeared, and the patient felt normal. Several months later, cortisone was stopped temporarily, and evidence of increased hemolysis appeared. In January, 1957, two years after HN_2 and the start of cortisone, the patient had a recurrence of fever and tender, painful adenopathy on the side opposite the original site. This focus was given roentgen-ray therapy, the local symptoms and fever disappeared, and the patient continues in remission up to the present time. Cortisone was temporarily discontinued again in March, 1957, and was reinstituted when it became clear that the hemolytic process still persisted but was under control with cortisone. The patient has had a palpable spleen during the entire period of observation.

We have observed remissions of varying lengths in Hodgkin's disease, lymphoma, and follicular lymphoma with steroid therapy alone, but do not recommend it for routine trial since HN_2 or x radiation therapy, or both, are more reliable. Furthermore, active Hodgkin's disease, especially, can be masked entirely with moderate amounts of steroids.

SUMMARY AND CONCLUSIONS

The management of the so-called "malignant" lymphomas, including Hodgkin's disease, follicular lymphoma, and lymphosarcoma, has been improved vastly by the addition of chemotherapeutic agents (nitrogen mustard and its derivatives) to the well-established procedures of surgical resection and roentgen-ray therapy. Such adjuncts as the sulfa drugs, antibiotics, and the hormones, ACTH and cortisone, have likewise contributed importantly in keeping these patients under clinical control during the responsive phase of their disease.

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THE MANAGEMENT OF MULTIPLE MYELOMA

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MULTIPLE myeloma is one of the most wretched diseases which afflicts man. The predilection of the disease to produce severe bone pain, bony fractures, anemia, bleeding, increased susceptibility to infections, hypercalcemia, and renal insufficiency is well known. Unfortunately, at the present time we are seldom able, except in the rare case, to accomplish other than symptomatic relief in this disease.

It is not the purpose of this paper to review the diagnostic aspects of multiple myeloma, since there are many recently published reviews,[1-6] but rather to discuss problems relating to treatment. Over the years a wide variety of agents has been used in an effort to bring about a remission, or at least palliation. X-ray, radioactive phosphorus, radioactive strontium, radioactive iodine, radioactive iodinated albumin, diamidines (stilbamidine, pentamidine, 2-hydroxystilbamidine), urethane, corticosteroids or ACTH, nitrogen mustards, 6-mercaptopurine, and 6-chloropurine have all been used. In general the result of therapy with these agents has been at best palliative, with only an occasional case demonstrating objective evidence of improvement, i.e., reduction in plasma cells in marrow aspirates, decrease in urinary and plasma protein abnormalities, healing of bony lesions, etc. Furthermore, it has not been demonstrated conclusively that any specific therapy will prolong life.

THE RELIEF OF PAIN

Almost uniformly every patient with multiple myeloma eventually begins to experience pain in his bones, whether it be true bone pain or that due to pathologic fracture of bone. Pain of the latter type is often the first manifestation of the disease, and it is this symptom which usually brings the patient to the physician. Fortunately, severe, racking, incapacitating pain is a late manifestation. Its exact cause is obscure, but treatment may be effective temporarily in controlling it. The physician frequently considers the use of narcotics (codeine, Demerol, morphine, etc.), which often provide rapid relief of pain. But because of undesirable side effects, nausea, vomiting, and constipation, and because they often have to be used in increasing doses, these drugs present difficulties in long-term management. Therefore, it is desirable to resort to other agents as soon

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as possible. We have been impressed in recent years with the value of the corticosteroids in the relief of bone pain.[7,8] Patients receiving large doses of narcotics can frequently be "weaned" away from them completely when under adequate corticosteroid dosage. The euphoria which some patients manifest and the diminished appreciation of pain are very gratifying when they occur. Caution should be exercised in the use of these drugs for it is well known that they may produce an increased susceptibility to infection (including tuberculosis), electrolyte imbalance, and ulceration of the gastrointestinal tract. It has been our custom to give adjuvant antacids to patients who have been receiving large doses of steroids, and not to give steroids when tuberculosis is a complicating disease. Electrolyte imbalance may be corrected by the dietary restriction of sodium and by the oral addition of potassium if edema or hypopotassemia occur.

Relief of bone pain may be accomplished in other ways. X-ray therapy judiciously administered for back pain is often helpful in alleviating this symptom if it is not due to compression fracture of a vertebra associated with nerve root compression. The explanation for the relief of pain by this type of therapy remains unclear.

Rather startling improvement in bone pain has been reported with stilbamidine,[1,9] urethane,[10,11] and radioactive phosphorus.[12] Unfortunately, we have encountered very few patients who have derived other than temporary relief of bone pain from these modalities of therapy.

BONE FRACTURE

Fracture of the weight-bearing bones presents a most difficult problem in management of this disease since it usually is a compression fracture of one or more of the vertebral bodies. It is a rare patient who ultimately escapes such a catastrophe. In addition, fractures of the femur, pelvic and iliac bones are frequently encountered. Mention should also be made of the difficult problem of sternal fracture. It may be inadvisable to carry out sternal bone marrow aspiration because of the possibility of producing a sternal fracture. The iliac crest is a preferable site for marrow aspiration when this disease is suspected. Although fractures of the clavicle, ribs, and arms occur, they usually do not pose as serious a threat to the patient as fractures of the sternum or of the weight-bearing bones.

It is perhaps a wise measure, if it can be accomplished economically, to carry out a roentgenographic skeletal survey of the weight-bearing bones at intervals to assess the extent of involvement so that pathologic fracture may be avoided as long as possible by proper orthopedic care. Patients should be cautioned about lifting heavy objects and engaging in activities which pose a threat to the integrity of the skeleton. Furthermore, orthopedic advice should be sought early in an effort to keep the patient up and about for as long as is feasible. The use of properly fitting back braces, crutches, etc., are often of great help. In general, we have not been impressed with the efficacy of surgical orthopedic intervention in this disease. Bone grafts, spine fusion, etc. are almost uniformly unsuccessful and may be fraught with serious hemorrhagic complications. External immobilization of a fracture may ultimately lead to stabilization of an involved bone.

but usually this is not of sufficient degree to permit resumption of weight bearing. Increased calcium intake, vitamin D, and testosterone, which have been suggested for the treatment of other types of osteoporosis, have not been useful in the correction of the bony demineralization so frequently encountered in this disease, and may possibly result in hypercalcemic crisis with all its attendant complications.

HYPERCALCEMIA

Skeletal decalcification in the form of discrete osteolytic lesions and generalized demineralization are common manifestations of multiple myeloma. Hypercalcemia may be associated with the hyperproteinemia, so characteristic of this disorder, because of the tendency of these proteins to bind calcium in increased amounts. More importantly, excessive bony destruction resulting from tumor growth may flood the blood stream with calcium at a more rapid rate than can be cleared by the kidneys. This complication may be observed in other malignancies involving bone, or in hyperparathyroidism. Serious and disabling signs and symptoms may result from high levels of serum calcium. Early recognition of the hypercalcemic state is important since, if it is not recognized and treated promptly, the patient may die of the consequences of hypercalcemia per se.

Hypercalcemia (serum values above 12 mg. per cent) is encountered in approximately 50 to 60 per cent of reported cases of multiple myeloma.[13] On the other hand the hypercalcemic syndrome[14,15] is encountered less frequently and is characterized by anorexia, nausea, vomiting, apathy, weakness, polydipsia, polyuria, intractable constipation, and drowsiness. The more severe cases may exhibit disorientation progressing to coma which ultimately may be accompanied by vascular collapse and result in death. Unfortunately, the hypercalcemic syndrome is difficult to recognize clinically in its early stages. Increased excretion of calcium in the urine may precede the signs and symptoms of this syndrome.[16] A rising level of serum ionized calcium is associated with the characteristic signs and symptoms, but the level at which symptoms develop may vary considerably from individual to individual.

Immobilization, pathologic bony fracture, and renal impairment are factors involved in the production of the hypercalcemic syndrome.[7,14] Immobilization of the patient, which frequently occurs in this disease because of bony fracture, can be a significant contributing factor by depriving the patient of the stimulus for new bone formation. Pathologic fractures may contribute to hypercalcemia as a direct result of bony dissolution at the fracture site. Decreased renal function, a common feature of multiple myeloma, may impair calcium excretion and thereby hypercalcemia may develop more readily. In some patients, with long-standing or severe hypercalcemia, calcium deposition may occur in renal tubules and further contribute to renal impairment.

The early recognition of the hypercalcemic syndrome is important in preventing some of the serious manifestations of this disorder, which should be suspected when any of the previously mentioned symptoms are encountered. A serum calcium determination in such a patient may confirm the presence of hypercalcemia before serious complications appear. Active therapy of the hypercalcemic syndrome may include one or more of the following.

1. High Fluid Intake.—A high fluid intake is an important therapeutic measure in the prevention and therapy of hypercalcemia.[15] Usually parenteral fluids are required because of the nausea and vomiting commonly experienced in this disorder. A high fluid intake provides the kidneys with sufficient fluid to insure continued and increased urinary excretion of calcium. In addition, dehydration and electrolyte imbalances which may occur are corrected by the administration of the appropriate parenteral fluid required to supply the patient's individual needs. When the patient's hypercalcemia is corrected, continued high intake of oral fluids may assist in preventing its recurrence.

2. Low Calcium Diet.—In the hypercalcemic state, elimination of high calcium-containing foods such as milk and other dairy products may be of benefit. In the severe case, however, the patient's symptoms of nausea and vomiting may preclude oral intake altogether, and under such circumstances parenteral feeding should be resorted to until vomiting has ceased.

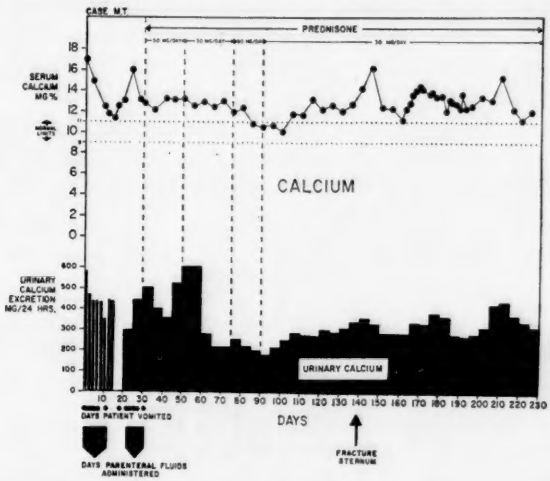

Fig. 1.—Chart showing serum calcium levels and urinary calcium excretion in a patient with multiple myeloma treated with prednisone. Metabolic balance was studied from the twentieth through the two hundred thirtieth day. Dietary intake of calcium was constant at a level of 353 mg. per day (average of dietary calcium determinations on duplicate diets prepared every 5 days) from the thirty-first through the one hundred sixty-fifth day. Dietary calcium was maintained at 1,509 mg. per day from the one hundred sixty-fifth through the two hundred thirtieth day. Fluid intake remained constant at a level of 2,600 c.c. per day from the thirty-first through the one hundred seventy-second day and 3,500 c.c. from the one hundred seventy-third through the two hundred thirtieth day. Parenteral fluids administered on the days indicated varied between 4,000 and 4,500 c.c. per day.

3. Corticoids and ACTH.—Cortisone, hydrocortisone and their analogues, or ACTH may be beneficial in several ways in the therapy of multiple myeloma. We have demonstrated that the symptoms and signs of hypercalcemia may be diminished by administration of adrenal steroids or ACTH. The explanation of the effectiveness of these agents in the correction of the hypercalcemic state is unknown, but at times their use is associated with a fall in serum and urinary calcium values (Fig. 1).

4. Sodium Citrate.—Sodium citrate may be of benefit in the very acute severe case by causing temporary reduction in the amount of ionized calcium in

the blood by formation of a soluble nonionized calcium citrate complex.[17] If improvement does not become evident, 250 c.c. of 2.5 per cent sodium citrate may be given slowly intravenously and repeated in 4 to 6 hours, or it may be given to the point of impending tetany as manifested by the development of the Chvostek sign.[14] Adequate renal function is imperative as alkalosis may be produced if kidney function is impaired. The latter may be as serious as the hypercalcemia.

5. Chelating Agents—Na EDTA and Sodium Phytate.—Sodium ethylene diamine tetraacetic acid, a substance which chelates calcium, has been used in the treatment of hypercalcemia occurring in various malignant diseases affecting the skeleton. It may be given intravenously in a 20 per cent solution diluted to 500 c.c. of glucose in water over a period of 4 hours as recommended by Spencer and associates.[18] This substance may also be given by mouth in an effort to decrease the amount of calcium absorbed or reabsorbed from the gastrointestinal tract. However, it should be pointed out that as yet insufficient data exist to recommend that this agent be used routinely. Also, it has been shown that administration of EDTA may have a serious nephrotoxic effect.[19]

Sodium phytate has also been given orally in an effort to suppress urine and serum calcium levels in patients with manifest hypercalcemia.[20] This substance may prove to be an effective agent provided that medication can be taken orally.

Of all the methods used to combat hypercalcemia it is our experience that proper hydration, perhaps coupled with steroid therapy, is the most effective means of dealing with this problem.

CASE REPORT

The following is a case report of a patient with multiple myeloma who developed hypercalcemia. It is presented to emphasize the hypercalcemic features which may be associated with the disease.

M. T. was a 48-year-old woman who was found to have narrowing and deformity of the thoracic vertebral segments, from T_4 through T_9, following the lifting of a heavy object. She was admitted to the hospital in August, 1955, when the diagnosis of multiple myeloma was established. X-rays revealed a large destructive area in the right ilium in addition to a diffuse osteolytic process throughout the skeleton. Bone marrow aspirates contained numerous plasma cells. Elevated serum globulin levels were found, and on electrophoresis an abnormal peak was demonstrated in the gamma globulin zone. A back brace was constructed, but it was impossible to get the patient out of bed because of pain. Despite continued efforts, she remained bedridden throughout the remainder of her life. Two weeks following admission she gradually became lethargic and developed frequent episodes of nausea and vomiting. Her serum calcium was found to be elevated to 16.9 mg. per cent. Renal function tests including blood urea nitrogen, serum creatinine, endogenous creatinine clearance, and para-aminohippuric acid clearance were all normal. Serum phosphorus, sodium, and potassium were also within normal limits. It was felt that the patient was suffering from the hypercalcemic syndrome and initial therapeutic efforts were directed toward increasing her fluid intake. She was given large quantities of intravenous fluids varying from 4,000 to 4,500 c.c. per day consisting of normal saline and 5 per cent dextrose in distilled water. Because of repeated vomiting and inability to take food or fluids by mouth, her serum potassium gradually began to fall, and it became necessary to supplement the infusions with potassium chloride. On this regimen her urine calcium excretion was high, varying from 348 to 582 mg. per 24 hours. Within 12 days the patient's serum calcium fell to 11.7 mg. per cent. At that time she was no longer lethargic and resumed her normal oral intake of food and fluids. Two weeks later, however, she again developed symptoms of hypercalcemia and was found to have a serum calcium of 15.9

mg. per cent. Return of the hypercalcemic state was thought to be related to persistent polyuria and her inability to ingest sufficient quantities of fluids to maintain positive fluid balance. Large quantities of intravenous fluids were resumed and her serum calcium again fell to 12.8 mg. per cent over a 7-day period. At this time she was started on prednisone (Meticorten*) therapy in divided doses of 50 mg. per day. She was observed while on continuous metabolic balance studies for a total of 210 days (Fig. 1). Later, prednisone was decreased to 30 mg. per day. During most of the balance study while the patient received prednisone, the serum calcium was only slightly elevated (except at the time the pathologic fracture occurred), despite the gradual progression of her disease. At no time during the entire period of prednisone therapy did she again develop symptoms of hypercalcemia. During the first two-thirds of the study the patient received a diet low in calcium and during the last one-third one high in calcium. Despite these dietary variations she was found to be in continuously negative calcium balance throughout the entire study. The fecal excretion of calcium was greatly increased on the high calcium diet, while the urinary excretion of calcium remained approximately as it had been when calcium intake was low. At no time during the study did the patient develop evidence of renal impairment. Following the metabolic balance studies she was given a trial of ACTH therapy, but her disease gradually progressed, and the patient ultimately died 9 months following her admission.

Comment.—This case demonstrates the effectiveness of a high fluid intake and the use of adrenal steroids in the management of the hypercalcemic state. The authors have studied several similar patients with hypercalcemia in whom this therapy also proved effective.

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INCREASED SUSCEPTIBILITY TO INFECTION

In the days before antibiotic therapy, one of the commonest causes of death in multiple myeloma was the development of an intercurrent infection. Pneumonia, sepsis, urinary tract infections, and cutaneous infections frequently led to the early demise of patients with this disorder. It is of some importance to reflect on the causes of the decreased resistance to infection noted in this disease. Several investigators have shown that many patients with myeloma exhibit a poor antibody response to various antigenic substances.[21,22] This is further substantiated by the observation that whenever the gamma globulin fraction is not obscured by a large abnormal component, it is almost invariably low or even absent.[4] A further reason why these patients are prone to develop infections is that they are often confined to bed because of pathologic fracture and fall prey to hypostatic pneumonia, pressure decubiti, and urinary infections. While it is well recognized that fever may occur in this and other malignant diseases, the fever usually represents an inflammatory process which may demand a prompt clinical and bacteriologic diagnosis so that the proper antibiotic therapy may be instituted. We have been impressed in our series of patients with the frequency of *Escherichia coli*, Pseudomonas, Proteus, and staphylococcus infections. Since the spread of infection is often rapid in myeloma, it may be necessary to institute antibiotic therapy after appropriate bacteriologic studies have been instituted but before cultural results are known. Although such "blind therapy" may not be considered good medicine in diseases uncomplicated by the malignant state, we have been impressed that it may be a life-saving measure in this malignancy. This is particularly important in the case of sepsis with gram-negative

*Meticorten was kindly supplied by the Schering Corporation.

bacteria which may be accompanied by profound cardiovascular collapse due to endotoxins elaborated by these organisms. Early and effective treatment is important also because of the early formation of collections of exudate which may be difficult, if not impossible, to eradicate even with well-designed treatment. In this, as in other diseases, careful bacteriologic cultural studies and antibiotic sensitivity tests are of great importance in determining proper antibiotic therapy.

ANEMIA AND HEMORRHAGE

An almost invariable finding in multiple myeloma is the presence of a normochromic, normocytic anemia. The occurrence of a normal red blood cell count and hemoglobin value is rare and the coexistence of polycythemia rarer yet. Hemoglobin values ranging between 6 and 10 Gm. per cent are frequently observed and without therapy of any type are often noted to be relatively stationary for months and even years in some patients. These individuals seem to adapt to an anemia of even moderate severity. It is often the tendency of the physician to consider that blood transfusions are indicated when he first discovers that the patient's hemoglobin is reduced. However, it should be emphasized

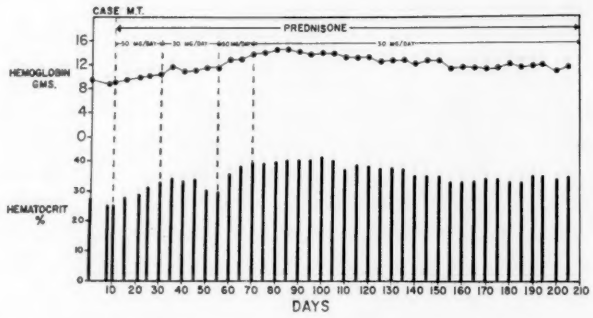

Fig. 2.—Chart showing the effect of prednisone on the hemoglobin and hematocrit values in a patient with multiple myeloma.

that transfusion is often not only of very transient benefit but that it carries with it certain inherent hazards. When the anemia is severe and the patient is symptomatic therefrom, or the patient is actively bleeding, transfusion may become a necessity. We have not found that the use of hematinics such as iron, liver, or B_{12} are useful in combating the anemia so commonly encountered. Steroid therapy may result in increases in hematocrit and hemoglobin values in this disease (Fig. 2).

Hemorrhagic tendencies are seen rather frequently, as previously reported by one of the authors.[23] Fortunately, however, bleeding is usually not severe. It may arise from a variety of causes, that is, thrombocytopenia, AC globulin deficiency, interference with conversion of fibrinogen to fibrin by the presence of the abnormal plasma protein component, cryoglobulinemia, macroglobulinemia, and the nonspecific interference of hyperproteinemia with the formation of an adhesive inelastic clot. It is difficult, if not impossible, to treat the hemorrhagic

diathesis of multiple myeloma. If epistaxis is a prominent feature, local measures such as astringents, pressure packs, topical thrombin, and cauterization may prove efficacious. If thrombocytopenia is present it may prove useful to employ ACTH or one of the adrenal steroids in an effort to combat hemorrhage due to this cause. Finally, the transfusion of fresh whole blood is sometimes of benefit when a specific plasma clotting factor has been found to be deficient or absent.

DRUG THERAPY

As noted previously, many agents have been tried in the treatment of this disease. Although interesting information has evolved from the use of certain modalities of treatment (i.e., the intracytoplasmic precipitates noted in the plasma cells of patients given stilbamidine[24]) only two drugs, urethane[10,11,25] and adrenal steroids,[7,8,26-29] have occasionally been noted to produce objective evidence of improvement and hence only these two drugs will be discussed. Some drugs such as stilbamidine have been found to be highly toxic[30-33] and accordingly have been discarded by many clinics.

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Urethane was first used in the treatment of multiple myeloma by Alwall in 1947,[34] and by Loge and Rundles in 1949.[10] These early observations were very encouraging and the hope became widespread that at last an effective agent had been discovered which would prove effective in many patients with this disease. Such has not proved to be the case. Over the past 9 years we have treated with urethane 15 patients in whom it was considered that a fair evaluation of the drug could be made (200 to 300 Gm. given in a period of 2 to 3 months). In only 2 patients was there objective evidence of improvement including regression in proteinuria, decrease in hyperglobulinemia, and a reduction in the number of plasma cells in marrow aspirates. The latter means of judging efficacy of therapy is admittedly a tenuous one because of the patchy nature of the infiltration of the marrow in this disease. In neither of our 2 patients who improved while on urethane were we able to demonstrate recalcification of lytic bone lesions. From the published reports there is little doubt, however, that this occasionally occurs.

Toxic effects of urethane include severe gastrointestinal disturbances—anorexia, nausea, and vomiting; leukopenia, thrombocytopenia, and hepatic damage. The gastrointestinal symptoms frequently preclude the administration of an adequate amount of the drug and are by far the commonest of the difficulties encountered. Several techniques have been suggested to avoid such distressing symptoms. The drug may be given in initially low doses of one gram per day, gradually increasing the dose to 4.0 to 6.0 Gm. per day, if tolerated. The oral administration of urethane may be accomplished by giving the water-soluble crystals either as a 10 per cent aqueous solution flavored with syrup, or in enteric coated tablets which contain 0.3 or 0.5 Gm. It should be pointed out however that the absorption of the latter form of medication may be erratic, for we have noted at times that the undigested tablets may appear in the stool unaltered. It is usually considered that a course of treatment with urethane consists of a total of 200 to 300 Gm. given in a period of 2 to 3 months. Other techniques which have been employed to combat the gastrointestinal manifestations of this

drug include giving the drug with meals, rectal administration of urethane suppositories, or intravenous administration in the same dosage levels as those given orally. The intravenous medication may be prepared in sterile saline and added to a 1,000 c.c. bottle of physiologic saline or 5 per cent dextrose in distilled water, and given slowly over a course of 8 to 10 hours. Other adjuvants such as chlorpromazine may be tried to combat the nausea and vomiting often associated with urethane administration.

It is advisable to give urethane in the prescribed course as outlined above. If no beneficial results have been detected at the end of 2 to 3 months of adequate therapy, or if severe toxic effects are noted, the drug should be discontinued. On the other hand, if beneficial effects are noted, the problem of prolonged administration, perhaps at lower dosage levels, arises. In our experience prolonged "suppressive" therapy of this type has yielded no better results than those obtained by interrupted treatment.

Leukopenia of variable degree may result from the administration of urethane. Four patients in our series developed a profound leukopenia (less than 1,000 white blood cells per cubic millimeter) while taking the drug, but in all cases when the drug was stopped the white blood cell count rose to normal levels. We do not consider that moderate leukopenia (3,000 to 4,000 white blood cells) demands that the drug be stopped. Thrombocytopenia, however, is a much more serious complication, and when it occurs in the course of therapy, urethane should be stopped and should not be reinstituted. We have seen no cases in which the development of liver disease could be definitely ascribed to this agent, but cases have been reported.[1,35]

In summary, it may be said that occasionally marked improvement may result from urethane administration in this disease. The erratic results encountered may be the result of many uncontrollable factors, i.e., toxic reactions which preclude the administration of the drug in adequate dosage over a long period of time, variation in absorption of the drug and, in extensive disease, a mass of tumor tissue so great as to render the drug virtually ineffective in its control.

Thorn, in 1950,[26] reported the first observations on the effect of ACTH in multiple myeloma and noted profound changes in the globulin levels. In the same year we reported[36] similar observations in 2 patients who were treated with ACTH. Since that time we have collected observations on an additional 26 patients who have been given ACTH, cortisone, prednisone, or combinations thereof. In none of these cases have we been able to demonstrate unequivocal evidence of regression of osteolytic lesions (with one possible exception). Undesirable side effects such as exogenous Cushing's syndrome, hypopotassemia, bacteremia and other infections, hypertension, thrombophlebitis, and gastrointestinal hemorrhage have been noted. Viewing the situation from the beneficial results obtained it should be stated that in almost every instance there has been a decrease in bone pain. Because of the euphoria the patients uniformly have felt better for long periods of time while receiving these agents. In 18 patients we have been able to demonstrate a marked decrease in the abnormal globulin components of the serum (measured electrophoretically) and this is associated with a decrease in proteinuria if the latter is present. The hypercalcemic syn-

drome may be reversed (as noted in a previous section of this paper). In 50 per cent of the cases we have been able to demonstrate a substantial rise in hemoglobin and hematocrit values. We have not been able to demonstrate definite evidence of decrease in the number or character of the plasma cells in the bone marrow.

At the present time we use between 30 and 50 mg. of prednisone, given in divided doses throughout the day, only when signs and symptoms would seem to warrant its use. It is not our custom to treat the asymptomatic disease with urethane or steroids.

RENAL INSUFFICIENCY

Renal insufficiency is not an uncommon terminal complication of multiple myeloma. The pathophysiology of the renal effects has been reported in detail.[37,38] Since we are unaware of any particular therapeutic measures other than those usually employed in the conventional therapy of uremia, this aspect of the problem will not be discussed. In our experience the occurrence of progressive uremia in multiple myeloma usually heralds an early demise of the patient.

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SUMMARY

The management of multiple myeloma has been discussed. Conservative measures which may be helpful in the care of the patient with this disease have been outlined. So-called specific drug therapy in this disease leaves a great deal to be desired and still provides wide opportunity for continued search for more effective agents.

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